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CLEARANCE OF PRODIGIOSIN DUST FROM THE RESPIRATORY TRACT OF NORMAL AND X-IRRADIATED RABBITS

GEORGE V. TAPLIN, M.D., JAMES S. GREVIOR, M.D.
CAMILLE FINNEGAN and ARTHUR DUNN

West Los Angeles, California

ONE of the major mechanisms by which the respiratory tract clears itself of insoluble particulate matter is by action of its ciliated cells. The posterior two thirds of the nose and the tracheobronchial tree, with the exception of the pulmonary alveoli, are lined with ciliated epithelium. The major function of these cells is to move the overlying film of mucous and foreign material toward the oropharnyx.[1,4,12] Ciliary action is continuous and dynamic. It is accelerated by irritants, moisture, elevated local body temperature, and alkaline secretions and is depressed by acidic secretions, cold, and dryness.[9] Ciliary movement may be altered by the local action of various drugs[2,8,11,15] and by the effects of ionizing radiation.[3,6]

In reviews of the modern literature on ciliary activity, the importance of this physiological defense mechanism has been stressed and demonstrated by numerous investigators[1,4,9,12] for more than twenty years. However, there is a paucity of quantitative data on respiratory tract clearance. A knowledge of the rate and efficiency of respiratory tract clearance is essential in assessing the inhalation hazard in atomic warfare, in industrial medicine, and in allergic respiratory diseases. Therapeutically, it is important to have basic information on the removal of medicated aerosols employed for their local action on the respiratory mucous membranes. Also, in radiation therapy of respiratory tract infections,[10] the beneficial effect of ionizing radiation on the clearance of pathological material from the

From the Atomic Energy Project, School of Medicine, University of California at Los Angeles.

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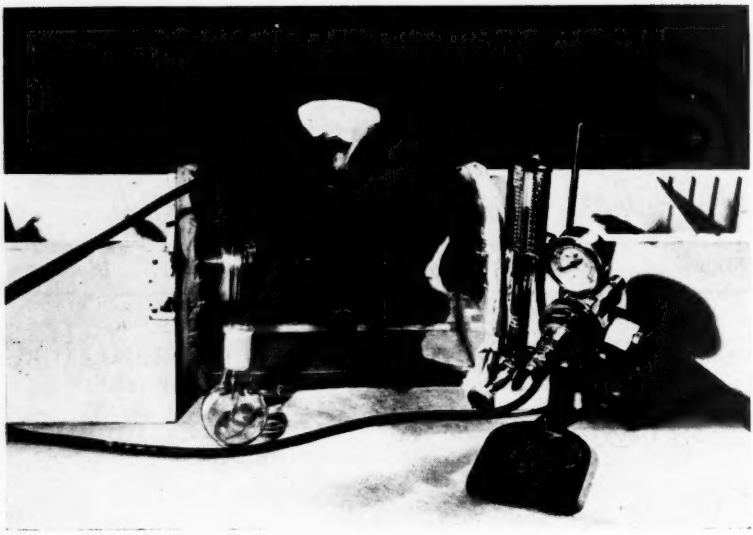

Fig. 1.

tracheobronchial tree may support the rationale for this type of therapy in those disease states which would be alleviated by improved clearance.

In this report data are presented from experiments on normal and X-irradiated rabbits, wherein the animals were given a single inhalation exposure to water insoluble prodigiosin dust[7] and sacrificed after increasing time intervals to determine, first, the distribution of the dye in various parts of the respiratory tract, and second, the rate and efficiency of its removal.

EXPERIMENTAL

Inhalation Procedure and Equipment: Dutch rabbits weighing 1.5 to 2.0 kg were exposed in pairs to an atmosphere of prodigiosin dust for thirty-minute periods. The amounts of prodigiosin deposited in the nasal mucosa, trachea, and lung parenchyma were determined quantitatively in each of these areas. Tissues were removed, weighed and extracted with acid chloroform, and the prodigiosin concentration per gram of tissue was measured by spectrophotometric analysis. The details of the extraction procedure and the method of analysis have been reported in a separate communication.[14]

The inhalation exposure chamber and the dust-producing apparatus used are shown in Fig. 1. The cylindrical lucite dust chamber is fitted at each end with perforated rubber diaphragms, which permit the insertion of the rabbits' head. Two animals are placed in restraining boxes, each adjacent to an end of the chamber. Dust is directed into the chamber between the two animals' heads and leaves at an opening at the top. This outlet is

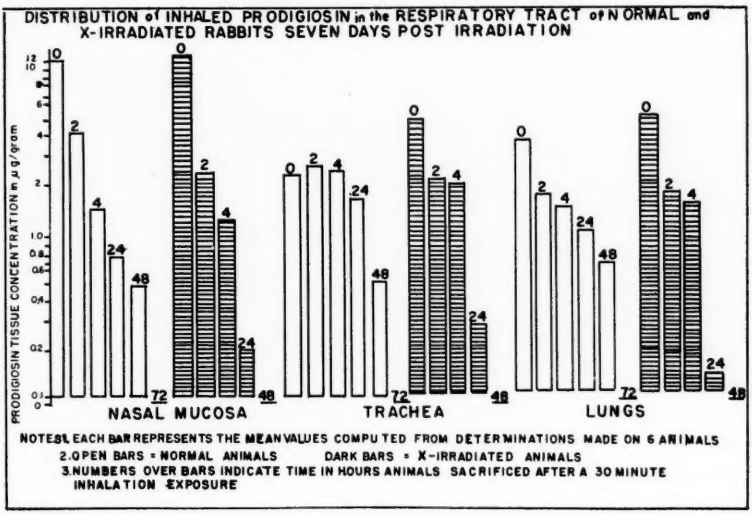
DISTRIBUTION of INHALED PRODIGIOSIN in the RESPIRATORY TRACT of NORMAL and X-IRRADIATED RABBITS SEVEN DAYS POST IRRADIATION
PRODIGIOSIN TISSUE CONCENTRATION in μg/gram
NASAL MUCOSA
TRACHEA
LUNGS
NOTES: 1. EACH BAR REPRESENTS THE MEAN VALUES COMPUTED FROM DETERMINATIONS MADE ON 6 ANIMALS
2. OPEN BARS = NORMAL ANIMALS DARK BARS = X-IRRADIATED ANIMALS
3. NUMBERS OVER BARS INDICATE TIME IN HOURS ANIMALS SACRIFICED AFTER A 30 MINUTE INHALATION EXPOSURE

Fig. 2.

provided with a simple filtering device which retains particulate material but permits free circulation of air.

The dust producer was operated by a constant flow of compressed air regulated at a rate of 7 liters/minute. It utilized the principle of elutriation plus centrifugal turbulence. Heavy particles were largely retained in the bulb, whereas fine particles were delivered from the outlet tube. The tubing connecting the dust producer to the inhalation chamber also acted to remove most of the remaining large particles escaping the dust producer.

In all experiments to be reported, the quantity of powder, its composition, the duration of exposure, and the flow rate were held constant. *Preparation of Micropowdered Prodigiosin:* Crystalline prodigiosin base* was mixed with powdered mannitol and ascorbic acid in the following proportions:

Prodigiosin	5 mg
Ascorbic acid	50 mg
Mannitol	1.0 g

Multiple quantities of this mixture were pulverized in a motor-driven mortar for two hours. The powder was then passed through a 200-mesh sieve to remove large sugar particules. The particle size distribution of the prodigiosin in the mixture was determined microscopically with a Filar micrometer after removing the soluble materials. By light microscopy the particle size range was between 0.5 and 3.0μ, while electron miscroscope

*Obtained through the courtesy of Dr. Arthur Lack, Birmingham Veterans Administration Hospital, Van Nuys, California.

measurements gave a range of 0.04 to 3.0μ. However, most of the particles were smaller than 0.5μ.

RESULTS

Distribution and Respiratory Tract Clearance Studies in Normal Rabbits: A series of thirty-six rabbits was subjected in pairs to an atmosphere of prodigiosin dust for single inhalation exposures. Groups of six animals each were sacrificed by air injection, immediately and after intervals of two, four, twenty-four, forty-eight, and seventy-two hours. The entire nasal mucosa was dissected, and the trachea and lungs were removed. The organs were weighed, minced, and ground in a Waring blendor with measured volumes of acid chloroform to extract prodigiosin. The results of these distribution and clearance studies are shown graphically (open bars) in Fig. 2. This bar graph demonstrates the relative amounts of prodigiosim dust initially deposited and retained in the three major parts of the respiratory system. It is apparent that the nasal mucosa contains a relatively large amount of the total dye retained, when values are calculated according to weight of prodigiosin per gram of tissue. The fact that a significant fraction of the total quantity deposited in the respiratory tract was found in lung tissue demonstrates that fine particles penetrate the pulmonary tree deeply and appreciable quantities are initially retained following a single short dust exposure.

The diminishing values of prodigiosin present in the three parts of the respiratory system of normal animals after increasing intervals indicate the rate and efficiency of the clearance mechanisms. It is apparent that these insoluble dust particles are removed more rapidly and effectively from the nasal passages than from the tracheas and the pulmonary parenchyma.

Effect of Ionizing Radiation on the Clearance of Prodigiosin Dust from the Respiratory Tract in Rabbits: The effect of whole body roentgen irradiation (800 r)** on respiratory tract clearance was studied because it is possible, in the event of atomic warfare, for persons to be injured by the initial gamma radiation, and subsequently exposed to dusts or mists containing fission products.[13,16] In such individuals, a knowledge of the effect of external gamma radiation on the respiratory tract clearance mechanisms might assist in the evaluation of the inhalation hazard as well as in prescribing effective emergency therapy.

On the seventh post-irradiation day, thirty-six animals were subjected to an atmosphere of prodigiosin dust, and groups of six were studied using the same serial sacrifice procedures employed with normal animals previously described. This post-irradiation interval and the 800 r dosage were selected because it is known that rabbits, under these conditions[5], frequently

**Radiation factors: 250 K.V. Picker Industrial X-ray unit, operated at 15 Ma, with a T.O.D. of 100 cm. Dosage administered at a rate of 76 r/min. X-ray beam filtered by .46 mm Cu and 1 mm Al. Animals exposed in groups of six and positioned in the field to obtain uniform dosage.

show evidence of radiation damage to the respiratory tract, characterized by increased nasal secretions, edema, and congestion of the entire respiratory mucosal epithelium, and by areas of pneumonitis.

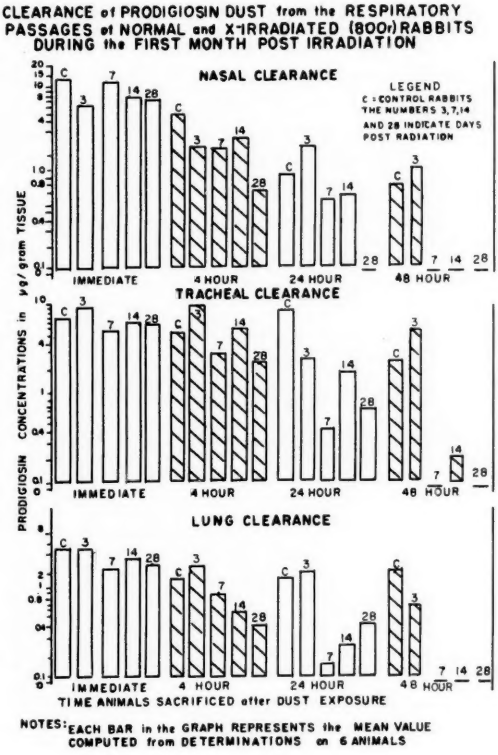
CLEARANCE of PRODIGIOSIN DUST from the RESPIRATORY PASSAGES of NORMAL and X-IRRADIATED (800r) RABBITS DURING the FIRST MONTH POST IRRADIATION
NASAL CLEARANCE
LEGEND
C = CONTROL RABBITS
THE NUMBERS 3, 7, 14 AND 28 INDICATE DAYS POST RADIATION
TRACHEAL CLEARANCE
LUNG CLEARANCE
PRODIGIOSIN CONCENTRATIONS in γg/gram TISSUE
IMMEDIATE
4 HOUR
24 HOUR
48 HOUR
TIME ANIMALS SACRIFICED after DUST EXPOSURE
NOTES: EACH BAR in the GRAPH REPRESENTS the MEAN VALUE COMPUTED from DETERMINATIONS on 6 ANIMALS

Fig. 3.

It was anticipated that the radiated animals might show impaired clearance. Apparently, the opposite effect is produced in rabbits. Both the rate and efficiency of the respiratory tract in removing insoluble dye particles are increased significantly by exposure to 800 r of whole body X-irradiation compared with similar data from normal rabbits (Fig. 2).

Similar Clearance Studies at Other Times During the First Month Post-Irradiation: Because the findings in the radiated group studied on the seventh day were contrary to predictions, similar experiments were designed to demonstrate the effect of whole body X-irradiation (800 r) on respiratory tract clearance after three, fourteen and twenty-eight days.

The experimental results are presented in Fig. 3. These data not only

confirm the seventh-day findings but also show that the entire respiratory tract clears itself even more quickly and efficiently at the fourteenth and twenty-eighth post-irradiation day intervals.

DISCUSSION

The information accumulated appears to be sufficient to state that 800 r of whole body X-irradiation in rabbits accelerates the rate and increases the efficiency of the respiratory tract clearance mechanisms. These defenses probably include several factors: namely, increased mucous secretion, stimulation of phagocytic function of the reticuloendothelial cells, and improved ciliary activity. The relative importance of each of these respiratory tract defense mechanisms cannot be evaluated separately from the available data. However, it appears from time factors that mucous secretions and ciliary action play a more significant role during the first one to two weeks than later. Further studies designed to demonstrate the relative parts played by ciliary action and mucous secretions separately from that due to phagocytic function of reticuloendothelial cells in normal and roentgen irradiated rabbits are being undertaken.

SUMMARY

The rate and efficiency with which the rabbit's respiratory tract removes inhaled insoluble particles has been determined by the use of prodigiosin, a dye which may be extracted from tissue specimens and measured accurately in minute quantities. All animals were given a single thirty-minute exposure to an atmosphere containing prodigiosin dust. By serial sacrifice techniques, it has been shown that the nasopharyngeal passages are cleared far more rapidly and completely than the lung parenchyma in both normal and roentgen-irradiated animals.

When rabbits are given 800 r whole body roentgen irradiation followed by a single inhalation exposure to prodigiosin dust, the removal of these insoluble dye particles from the nasal mucosa and from lung tissue is greatly accelerated and the efficiency of its clearance is definitely increased over that of the normal animal, especially at the fourteenth and twenty-eighth post-irradiation days. The probable clinical significance and the mechanisms of this beneficial effect from whole body X-irradiation are discussed, and the need for further investigation is stressed.

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Atomic Energy Project, University of California,
P. O. Box 4164, West Los Angeles

PROCEEDINGS OF FIRST INTERNATIONAL CONGRESS FOR ALLERGY

Announcement has been received of the publication of the Proceedings of the First International Congress for Allergy, edited by A. S. Grumbach, General Secretary, assisted by A. Rivkine, of the First International Congress for Allergy, held under the auspices of the International Association of Allergists. The Proceedings published *in extenso* contain 26 reports, 22 openers, all discussions and all 152 individual contributions presented at the Congress. All reports and individual contributions are published in the original text and supplied with summaries in two complimentary languages, French and German. The Proceedings will be a unique source of information. XXXII, 1143 p., 305 fig. Price $38.00 if order is received within six weeks of the announcement.

All of those who attended the First International Congress, particularly those who participated in the program, will want the book. It may be obtained by writing to the publishers, S. Karger, Holbeinstrasse 22, Basel, Switzerland.

Order now, as the edition is limited and there were 600 registrants at the Congress.

SOME INVESTIGATIONAL STUDIES CONCERNING REACTIONS TO INSECT BITES

EVELYN M. ROCKWELL, M.D.
Cincinnati, Ohio

EXPOSURE to the injection or deposition of foreign material by insects is a common experience. Hence it is not surprising that certain arthopods serve as vectors and intermediate hosts for many infectious diseases and that also bites by arthropods result in reactions from mechanical and chemical irritations and allergens. That the substance injected may be a primary irritant is exemplified by wasps, bees, ticks, and certain species of spiders. Likewise, foreign body reactions may result if bits of chitinous material are left behind, as exemplified by the tick.

Allergic reactions to the bites of arthropods should be expected since repeated parenteral injection of a foreign protein may produce the anaphylactic state. Ample proof has been reported to verify allergic reactions following bites by many arthropods,[5,7] including chiggers, fleas,[12,18] bedbugs, lice, bees, and mosquitoes.[4,6,15,16,17]

Our study concerns mainly mosquito bite reactions. It has been demonstrated that both early and late reactions may develop with repeated mosquito bites.[17] Decreased reactions likewise occur with repeated bites or injections of aqueous mosquito extracts. Passive transfer of the immediate reaction has been demonstrated.[6,16] Dubin et al[8] attempted to protect rabbits against mosquito bite reactions by three weekly subcutaneous injections of 5 cc of 1:1000 crude suspension of mosquitoes. Sensitization rather than protection resulted. Thus it has been demonstrated that reactions to mosquito bites can be allergic and based on specific sensitization.

STUDY OF EXTRACTS

Hecht[13] used unsterile extracts for scratch tests and concluded that the allergen was distributed throughout the body of the mosquito. We repeated his work using sterile extracts of (1) salivary glands from ten *Anopheles quadrimaculatus* per cc saline, (2) abdomens from ten *Anopheles quadrimaculatus* per cc saline, (3) legs and wings from ten *Anopheles quadrimaculatus* per cc saline. Intradermal skin tests with 0.02 cc of the above revealed that the largest immediate wheal was obtained with the abdomens and the smallest with the legs and wings (Fig. 1). On a w/v basis it was

From the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati.

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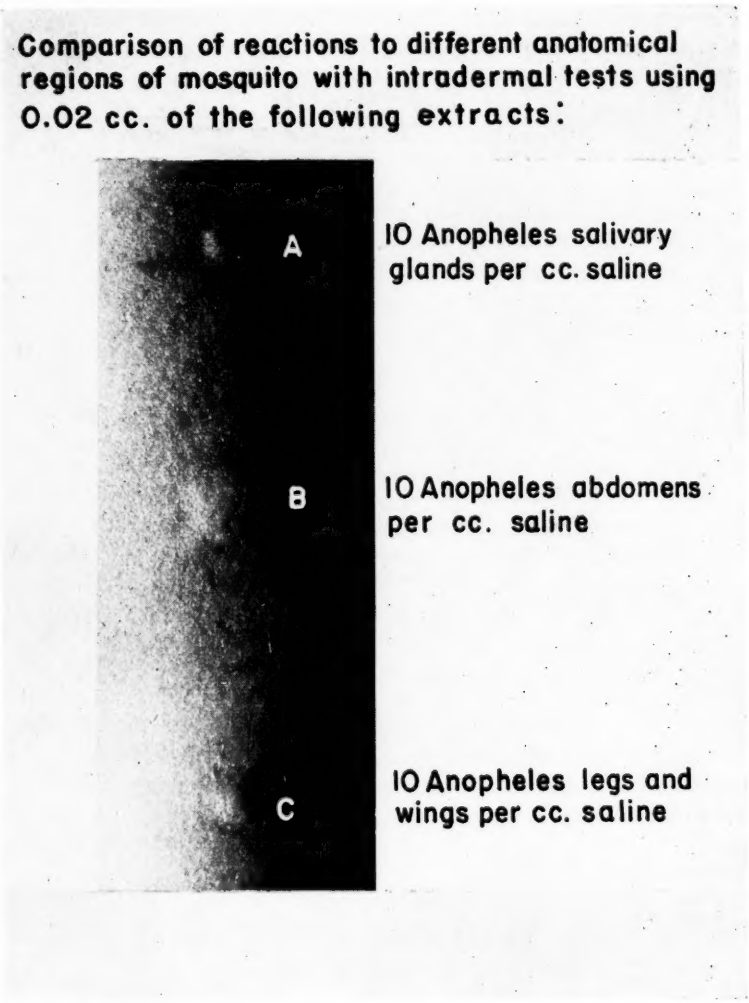
Comparison of reactions to different anatomical regions of mosquito with intradermal tests using 0.02 cc. of the following extracts:
A
10 Anopheles salivary glands per cc. saline
B
10 Anopheles abdomens per cc. saline
C
10 Anopheles legs and wings per cc. saline

Fig. 1.

found that an extract of *A. aegypti* legs and wings produced wheals in sensitive individuals identical to those produced with the same concentration of whole *A. aegypti*. Thus Hecht's original observations are confirmed.

For subsequent work, the mosquitoes were extracted in Coca's solution, the pH adjusted to approximately 7, and the extracts Seitz filtered and cultured for sterility. Fifty per cent glycerine was added except for tissue culture and animal work, and patch tests.

TABLE I. COMPARISON OF MOSQUITO BITE AND SKIN TEST REACTIONS

No. Pts.	% Pts. over 40 yrs. old	Reaction to Bites				Reaction to Extracts*					
		Aedes		Anoph.		1:000 Aedes		1:10,000 Aedes		1:10,000 Anoph.	
		Early	Late	Early	Late	Early	Late	Early	Late	Early	Late
5	80	neg.	neg.	4 neg. 1-2 cm w.	3 neg. 2 pap.	neg.	2 neg. 3 pap.	neg.	2 neg. 3 pap.	neg.	2 neg. 3 pap.
2	100	neg.	pap.	2 neg.	2 pap.	neg.	pap.	neg.	pap.	neg.	1 neg. 1 pap.
5	80	1 to 5 mm w.	neg.	4 neg.	4 neg.	4 neg. 1−+	2 neg. 3 pap.	neg.	2 neg. 3 pap.	neg.	2 neg. 3 pap.
5	100	1 to 5 mm w.	mac.	3 neg. 1-1 mm w.	2 neg. 2 mac.	2 neg. 3−+	pap.	4 neg. 1−+	pap.	neg.	1 mac. 4 pap.
23	48	1 to 5 mm w.	pap.	9 neg. 1-2 mm w. 2-1 cm w.	3 neg. 1 mac. 8 pap.	15 neg. 8−+	1 mac. 22 pap.	15 neg. 8−+	1 neg. 1 mac. 21 pap.	16 neg. 7−+	3 neg. 1 mac. 19 pap.
1	0	6+mm w.	neg.	neg.	pap.	+	mac.	+	mac.	neg.	mac.
4	75	6+ mm w.	mac.	2 mac. 1-5 mm w.	1 mac. 2 pap.	4−+	1 neg. 1 mac. 2 pap.	1−+ 3 neg.	1 neg. 1 mac. 2 pap.	neg.	1 neg. 3 pap.
12	25	6+ mm w.	pap.	1 neg. 2 mac. 4 w.	1 neg. 6 pap.	3 neg. 9+ to +++	1 mac. 11 pap.	5 neg. 7+ to ++	1 neg. 1 mac. 10 pap.	6 neg. 6−+	3 neg. 9 pap.

Code:
neg. = negative
w. = wheal
pap. = papule
mac. = macule

Aedes = Aedes aegypti
Anoph. = Anopheles quadrimaculatus
*All skin tests done intradermally using 0.02 cc extract

To evaluate the mosquito extracts, fifty-seven hospitalized patients were tested simultaneously with *A. aegypti* bites and the following extracts: 1:1000 *A. aegypti*, 1:10,000 *A. aegypti*, 1:10,000 *Anopheles quadrimaculatus*, dust, and control (1 per cent glycerine in saline). Thirty-eight of the patients were also tested with an *Anopheles quadrimaculatus* bite. Both immediate and twenty-four-hour reactions were recorded (Table I).

In summary there is good correlation between the immediate reactions to *A. aegypti* bites and 1:10,000 *A. aegypti* extracts, but this is not true of the late reactions. Whether these late reactions to the extracts in the absence of a late reaction to the bite are due to primary irritation or whether the allergenic content of 0.02 cc of 1:10,000 mosquito extract is greater than that injected by one mosquito is not known.

TOXICITY STUDIES

A. aegypti fed from the forearm of ten newborn babies. In four a 1 to 2 mm petechial reaction was noted immediately. Twenty-four hour readings were possible in nine cases, and in six there was a 1 to 2 mm red papule.

Gordon and Crewe[11] noted distinct hemorrhages and separation of collagenous fibers in biopsies of twenty-four-hour reactions to *A. aegypti* bites in guinea pigs not bitten previously and therefore state that the late reaction to mosquito bites is due to irritation. We noted that guinea pigs and rabbits not previously used for feeding mosquitoes reacted to *A. aegypti* bites with immediate and late 1 to 4 mm papules. Rabbits used daily for feeding a colony of *A. aegypti* showed only a slight erythema following bites. Thus a resistance to the primary irritation results.

In attempts to develop anaphylaxis in guinea pigs with mosquito extracts the following observations were made: guinea pigs given 3 cc of 1:10 *Anopheles quadrimaculatus* extract or 3 cc of 1:10 of the acetone precipitate of Anopheles extract intraperitoneally died in twenty-four hours. Two tenths cc of 1:100 *A. aegypti* extract administered intracutaneously resulted in anaphylactoid symptoms. Sprent[20] reported similar findings using tissues of *Ascaris lumbricoides* and attributed it to nonspecific protein shock.

Aedes aegypti extract was compared with a saline extract of dust and "Lyovac" Bee Venom Solution* for toxicity in tissue culture. Eight-day chick embryo heart tissue was cultured in hanging drop slides with a chick embryo extract and chick plasma clot. Various dilutions of the extracts were added directly to the clot, and outgrowth readings were made at forty-eight hours. Aedes inhibitory concentration was between 1:40 and 1:80 of the total clot. Dust inhibited outgrowth between 1:24 and 1:40; bee venom, between 1:6400 and 1:12,800 of the prepared solution. These results parallel the clinical observation that bee stings are more toxic than mosquito bites.

*Sharp and Dohme, Philadelphia—1 cc represents ten bee stings.

STUDIES OF SEVERE REACTIONS TO MOSQUITO BITES

Six patients with severe reactions to mosquito bites were studied. Four reacted with erythema and edema extending over an area up to six inches in diameter; one reacted with a late papulovesicular reaction; and one reacted with erythema and edema, central bullae, regional adenopathy, and a fever. Our findings were as follows:

1. All except one gave a personal and/or family history of eczema, asthma, or hay fever. Similar observations have been reported by Brown[6] and Benson.[2,3]

2. All of those tested with bites of other insects gave moderate to severe reactions to those insects to which they had been previously exposed. One of the patients came under our observation because of lichen urticatus from bedbug bites.

3. Biopsies from two of the patients showed an inflammatory infiltrate containing a large proportion of eosinophils and extending into the subcutaneous fat.[1,6,9] These findings are similar to local penicillin reactions produced by repeated intradermal injection of penicillin by Suskind and Simon[21] (Fig. 2).

4. All gave a positive immediate and/or late reaction to 1:100,000 or 1:1,000,000 *A. aegypti* extract. Thus these reactions were greater than those in the group of fifty-seven persons with mild reactions to mosquito bites.

5. Patch tests with 1:10 *A. aegypti* extract were positive in the two patients with vesicles or bullae following *A. aegypti* bites. Patch tests in seven controls were negative.

6. Serum from one of the patients was used for passive transfer of sensitivity to *A. aegypti* bites. In only one of ten nonreactors was it possible. Thus adequate receptors for passive transfer of sensitivity to mosquitoes are difficult to find. Perhaps the nine nonreactors who were not receptors of passive transfer had been hyposensitized by exposure and had developed a blocking mechanism which prevented passive transfer.

7. Leukocyte cultures with the addition of mosquito extract were done as a test for bacterial-type hypersensitivity through the co-operation of Dr. H. Blatt. Samples of leukocytes from three patients hyperreactive to mosquito bites were necrotized by *A. aegypti* extract in a concentration that did not necrotize the white blood cells of patients with none to mild mosquito bite reactions.

8. Hyposensitization was attempted in three of the patients, starting with 0.05 cc of 1:10,000,000 *A. aegypti* extract. Injections were given every three to five days until the maximum tolerated dose was reached, and this was repeated once weekly. Two of the patients have been followed two summers, and one, one summer. In all cases, the reactions became less severe but the patients continued to develop late papules following mosquito bites, and one of the patients developed severe erythema and

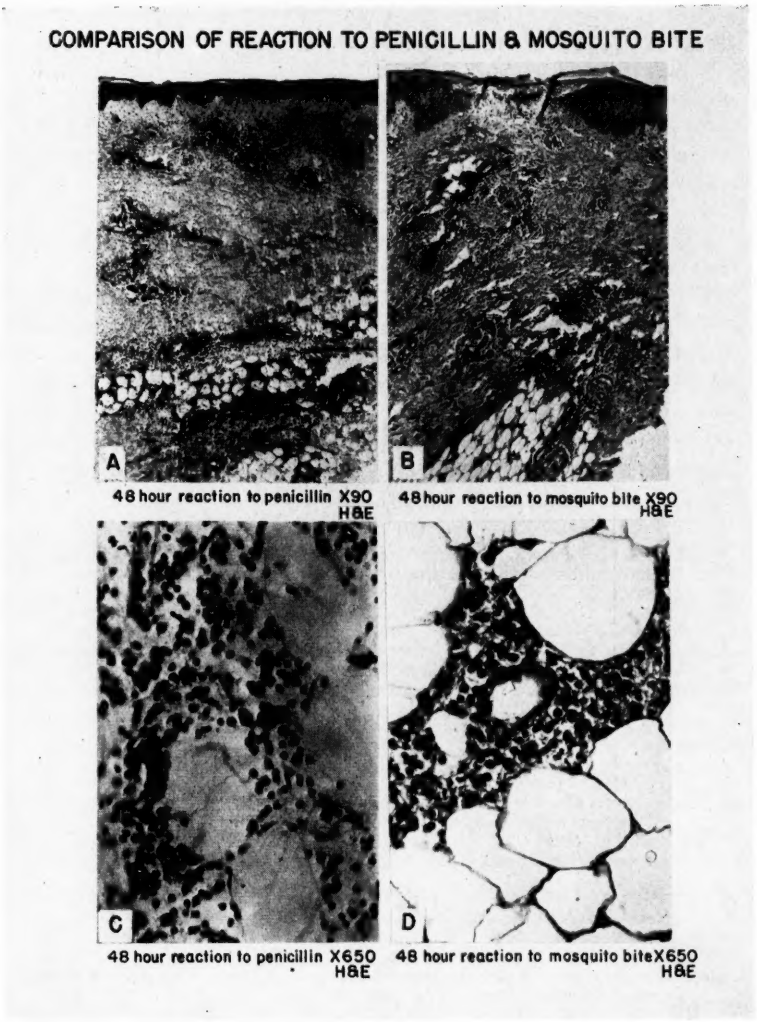
COMPARISON OF REACTION TO PENICILLIN & MOSQUITO BITE
A
48 hour reaction to penicillin X90 H&E
B
48 hour reaction to mosquito bite X90 H&E
C
48 hour reaction to penicillin X650 H&E
D
48 hour reaction to mosquito bite X650 H&E

Fig. 2. Reduced one half.

edema on two occasions when over a week elapsed since the last injection. One patient was followed with actual *A. aegypti* bites, and there was definite decreased reactivity.

We have observed persons with difference in reactions to different species of mosquitoes; and Hecht,[14,16] Mellanby,[19] and Heilesen[17] report similar observations. Yet using *A. aegypti* extract, we obtained apparent hyposensitization to the mosquitoes around Cincinnati, which are mainly *Culex*

pipiens. A possible explanation of this conflicting data is that multiple allergens are involved, some of which are species specific.

9. Cortone and adrenocorticotropic hormone administered systemically produced a variable inhibitory effect on mosquito bite reactions. Local cortone had no effect on mosquito bite reactions, but local Compound F was shown by Goldman[10] to have a persistent inhibitory effect on the bite reaction.

SUMMARY

1. Extracts of various portions of the mosquito produce similar reactions in sensitive individuals.

2. Small mosquito bite reactions can result from irritation alone.

3. Three clinical types of allergic reactions follow mosquito bites: urticarial, tuberculin, and eczematous.

4. A high percentage of persons with severe mosquito bite reactions give personal and/or family histories of other hypersensitivity reactions.

5. Our aqueous mosquito extracts are toxic in high concentration, but weaker concentrations are of value in the diagnosis and treatment of mosquito bite reactions.

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PAPULAR URTICARIA

Its Relationship to Insect Allergy

BERTRAM SHAFFER, M.D., and COLEMAN JACOBSON, M.D.
Philadelphia, Pennsylvania
and
PRIMO P. PORI, M.D.
Hazelton, Pennsylvania

THE purpose of this presentation is to attempt to demonstrate that some cases of papular urticaria are related to insect allergy and to detail a method of treatment based upon this etiologic concept. To substantiate this view we propose to outline some studies based upon clinical, epidemiologic, allergic, histologic, and therapeutic evidence contributed by others and by our group.

We wish to emphasize that insect allergy may be only one of a number of causes of this clinical syndrome. However, most of the cases that we have observed seem to be explainable on this basis.

CLINICAL PICTURE

Papular urticaria (lichen urticatus or urticaria papulosa) from its early description[3] down to modern textbook accounts[16,20] has always been discussed as a cutaneous clinical syndrome. Its identification and nosologic status, therefore, has been dependent solely on the descriptive features of the eruption and not necessarily on any etiologic, physiologic, or pathologic association. Indeed, papular urticaria generally occurs in individauls who otherwise appear to be in a relatively good state of health. The disease affects children predominantly, especially in the two to seven year age group. It is most rare in early infancy and in later childhood. In our experience, the young victims are usually members of the lowest social stratum. Negroes are particularly affected. Consequently, the disease is seen frequently in free children's clinics in large cities. In temperate climates it is seen with greatest frequency in the hot weather months.

The eruption tends to be distributed to the exposed (Figs. 1 and 2) portions of the skin, especially the extremities, head, neck, and shoulders. The genitalia, buttocks, webs of the fingers, and intertriginous sites are usually exempt. This is of great help in the differentiation of papular urticaria from scabies.

From the University of Pennsylvania Departments of Dermatology and Syphilology, School of Medicine, Donald M. Pillsbury, M.D., Director; Graduate School of Medicine, Herman Beerman, M.D., Chairman; The Skin and Cancer Hospital of Philadelphia, Bertram Shaffer, M.D., Medical Director; and the Department of Dermatology, Albert Einstein Medical Center, Southern Division, Bertram Shaffer, M.D., Attending.

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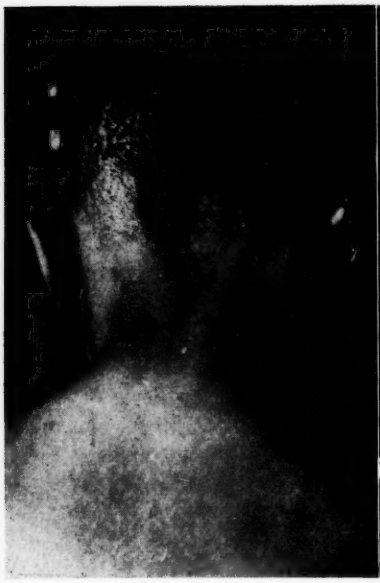

Fig. 1. Papular and papulo-nodular lesions of papular urticaria are grouped on the back of the neck of a Negro child, aged 4.

Fig. 2. Urticarial, urticario-papular and papular lesions are to be found on the legs and popliteals. Excoriative and impetiginized lesions are also apparent. Same patient as Fig. 1.

The basic individual lesions are discrete wheals and papules with all grades of transition between these two types. The wheals are transient, usually few in number, and sometimes they may be absent. The papules are numerous and persistent and at times seem to eventuate from preëxisting wheals. As the individual lesion ages, one sees variations from a bright red urticario-inflammatory formation through dull red to brownish, hard, fibrotic developments. These papules are the most important and the most characteristic lesions of the disease. Without their presence a definitive diagnosis of papular urticaria cannot be made. Occasionally one finds associated vesicular or bullous lesions and excoriative phenomena with or without impetiginization. These secondary manifestations may be so marked as to dominate the clinical picture and render the basic lesions difficult to detect.

Opinions have been expressed from time to time regarding insect bites as a possible cause of this disease.[6,14] but until the past few years no evidence was forthcoming to substantiate this contention. The evidence supporting this view is clinical, epidemiologic, allergic, histologic, and therapeutic. We detail herewith the pertinent available facts.

CLINICAL EVIDENCE

Bateman[3] in his description of papular urticaria stated that "its first appearance is in irregular, inflamed wheals, so closely resembling spots excited by the bites of bugs or gnats as almost to deceive the observer."

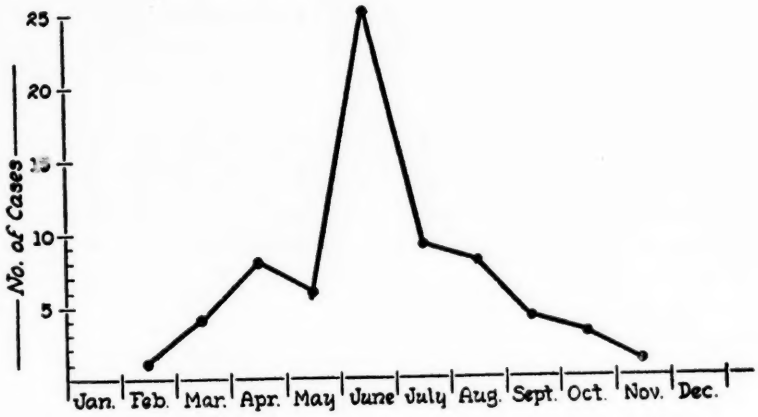

Fig. 3. Seasonal incidence of 69 cases of papular urticaria. (Taken from Shaffer, Spencer and Blank. J. Invest. Dermat., 11:293, 1948.)

Jonathan Hutchinson[14] was of the opinion that the disease might be produced by insect bites, as did also Ashby, Wright, Ashby, and Roberts.[1] Fox[10] commented on urtication preceding papulation. Chipman[6] was a strong proponent of the flea as the etiology of this condition. Goldman[11] suggested that insects were probably causative in nine cases of a total of twenty-seven of this syndrome that he studied. Lunsford[15] commented on the similarity between flea bits and papular urticaria and quoted from the literature several instances in which the diagnosis of flea bites and papular urticaria could be or was made on the same patient by different observers.

Our own group also felt that most cases of papular urticaria seen by theme were due to sensitivity to the bites of fleas and bedbugs.

EPIDEMIOLOGIC EVIDENCE

The seasonal incidence of this disease is most striking. It appears almost exclusively in the warm weather months, and it reaches its peak frequency in mid-summer.[17] (Fig. 3) Only rarely does one find a case of papular urticaria during the winter. In the Eastern United States it is during the summer months that biting insects are most active. It is well known, for instance, that human, cat, and dog fleas are most active during July, August, and September,[2,4,19,22] and that they are almost wholly absent from December 1 to May 1.[4] Bedbugs have no true seasonal incidence, but they sur-

vive the winter in a relatively quiescent state[2,22] with their activity especially reduced in ill-heated homes, where so many of the victims of this disease live.

A careful history in many cases of papular urticaria will reveal exposure to biting insects or the presence of sources of these insects. In the investigation of Blank, Shaffer, Spencer, and Marsh[5] "of 87 patients with papular urticaria, it was possible to elicit a history of known exposure to fleas in 26 cases and to bedbugs in 8 cases. In addition, possible exposure to these insects via the presence of cats, dogs, collections of sand and sand boxes was indicated in 72 cases."

Lunsford[15] in commenting on the prevalence of fleas and flea bites in southern California felt that most cases of papular urticaria seen by him were due to flea bites. This eruption occurred chiefly in children, or else it appeared in adults who were newcomers to the Coast. He felt that while endogenous paplar urticaria may exist, it is rare as compared to the exogenously produced flea variety. He noted that Jadassohn in Germany and Hallam, Tate and Kinnear in England, as well as Urbach in Vienna, all reported that papular urticaria improved when the patients were hospitalized but recurred when they returned home. These authors concluded that papular urticaria was an allergic manifestation and that the allergen was in the home, food, or bedding. They, however, failed to attribute this disease to insects which could well have accounted for the allergen present in the home environment but not in the hospital. Lunsford, himself, observed and he also quoted Kinnear and Templeton to the effect that papular urticaria often had its onsent after the patient moved from one geographical location to another. He pointed out that the etiologic insect agent of papular urticaria seems to have varied, depending upon the prevalent type of biting insect in the geographic area concerned. Goldman's observations[11] in Mexico led him to conclude that flies, fleas, chiggers, mosquitoes, Cimex, and Simulium are responsible for this syndrome in that country. He also felt that allergic reactions to scabies and pediculosis may at times result in this clinical picture.

In our locality (Philadelphia)[5,17] most cases of papular urticaria seemed to be related to insect infestation, especially to bedbugs and fleas.

ALLERGIC EVIDENCE

Papular urticaria, excluding insect allergy, has been studied extensively from the standpoint of allergic reactivity. Sidlick and Knowles,[18] Walzer and Grolnick,[21] and Cooke[7] found that, in general, these studies were inconclusive and the results did not lead to a uniformly satisfactory therapy. Apparently systemic skin testing with insect allergens had not been tried until the studies of Shaffer et al,[17] although Goldman[11] had tested three of his patients with fly antigen with negative results. Blank, Shaffer and Spencer[5] reported a high incidence of positive skin reactions of the delayed type to flea and bedbug antigen in cases of papular urticaria. They used

extracts made according to the method of Cherney by extracting dry pulverized insects with phenol 0.5 per cent in saline for forty-eight hours. These extracts were then passed through a "Swinny" type Seitz filter. The preparation was diluted 1:5,000 and 1:10,000 for flea and 1:5,000 for bedbug, calculated on the original dry weight of the insects used. The control solution was phenol 0.5 per cent in saline diluent.

Thirty patients with papular urticaria and 124 controls of the corresponding age group were tested.[5] Delayed (forty-eight hour) readings were made with the following results: (Fig 4)

Fig. 4. Results of skin tests to insect allergens on same patient shown in Figs. 1 and 2. Readings at 48 hours are: (1) control—negative, (2) flea—positive, (3) Stock silk antigen —negative, (4) Cimex—positive.

Nineteen patients had positive reaction to flea antigen, while ten patients reacted to Cimex antigen. Twenty-three of these (77 per cent) reacted either to flea or to Cimex antigen or both. Of the 124 control subjects there were only two positive tests, both of these to the Cimex antigen. Not reported hitherto, but subsequently observed, was the fact that some of our patients with papular urticaria give delayed positive reactions to mosquito antigen, and all of these patients as well as many in the control group gave immediate (urticarial) positive skin tests to insect allergens.

TABLE I. 70 NORMAL CHILDREN—URTICARIAL REACTIONS TO INSECT ALLERGENS
M—Mosquito F—Flea C—Cimex

Age groups (years)	0-1	2-3	4-5	6-7	8-9	10-12
Number of cases tested	12	10	10	17	13	8
Insect antigen	M F C	M F C	M F C	M F C	M F C	M F C
Number positive antigen	0 1 0	5 1 1	8 7 2	15 12 3	6 3 2	3 3 0
% positive antigen	0 9 0	50 50 10	80 70 20	88 70 24	60 30 15	37 37 0
Total number tests	36	30	30	51	39	24
Total number tests positive	1	37	17	30	11	6
% total tests positive	2.8	23.3	56.6	58.9	28.2	25.0

A study of such a control group (Table I) reveals the significant fact that urticarial reactivity to insect allergens (mosquito, flea, and Cimex in this experiment) is practically nonexistant during the first year of the patient's life. Thereafter, it rises sharply, reaching a peak between the fourth and the seventh year, after which it tapers off as the individual enters adolescence. The significance of this observation relevant to insect allergy and papular urticaria will be discussed later.

Dietrich[9] and Hamburger[12] studied the reactions of patients to papular urticaria by the placement of bedbugs and fleas directly on the patient's skin. They concluded that papular urticaria represented an unusual reaction to the bites of insects (in their cases, bedbugs, and fleas) and that this sensitivity developed early in life but disappeared at a later age.

HISTOLOGIC EVIDENCE

Jacobson, Shaffer, and Beerman[17] have studied histologically a series of cases of papular urticaria, presumably due to bedbug, flea, and mosquito bites. The etiology was based not only on epidemiologic evidence and the results of therapy but also on the study of skin tests.

Both the urticarial type lesions and the late papular lesions were examined. They also studied histologically positive skin tests of both the urticarial and the tuberculin type to insect allergen in these same patients. As controls, lesions and skin tests from other patients that would ordinarily be diagnosed as insect bites were examined. The results of this investigation emphasized the striking similarity histologically between insect bites, lesions of papular urticaria, and positive skin tests, provided these lesions were of the same clinical type: i.e, the early or urticarial type skin test resembled early insect bites and the evanescant lesions of papular urticaria. Positive skin tests of the tuberculin type resembled the inflammatory papular stage of papular urticaria.

THERAPEUTIC EVIDENCE

Before the concept of insect allergy as an important etiologic factor in papular urticaria was developed, the disease was, in general, resistant to treatment. Shaffer, Spencer and Blank[17] reported on the successful use of DDT* in papular urticaria. The later report by Blank, Shaffer, Spencer and Marsh included a larger series of cases.[5] (Fig. 5)

*Dichlorodiphenyltrichlorethane

The patients were treated by dusting lightly once a day with a powder consisting of 5 per cent DDT in talc, and the parents were given the following printed instructions:

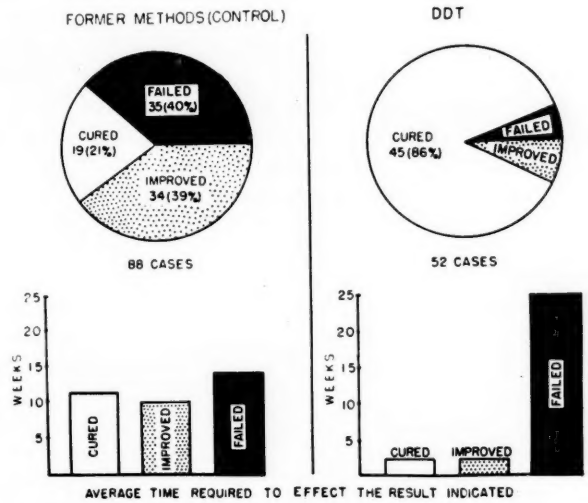

Fig. 5. Results of treatment of papular urticaria with DDT compared to other methods (from Blank, Shaffer, Spencer and Marsh: Papular urticaria: study of the role of insects in its etiology and the use of DDT in its treatment. Pediatrics, 5:408, 1950).

1. A spray of 5 per cent DDT in Flit is to be used daily in your household. The baseboards, the cellar, the bed frames, and upholstered furniture should receive special attention.
2. A powder of 5 per cent DDT should be dusted on dogs and cats, under cushions and rugs, and wherever the spray cannot be used.
3. Contact with dogs and cats should be avoided.
4. All collections of sand should be removed.
5. The child should be dusted lightly with the special powder which will be prescribed. This powder should also be dusted on his bed clothes and mattress.

Forty-six (86 per cent) of a group of fifty-four patients so treated in whom an appropriate follow-up was obtainable were "cured": i.e., they had no new lesions and there was a complete cessation of itching within two weeks. This compares favorably with a group of patients treated in preceding years by other methods where 21 per cent were "cured" only after a period of eleven weeks. It seems quite possible that most of the latter group were actually "cured" by nature with the termination of the hot weather season and the end of insect activity for that period.

THE GENERAL PRINCIPLES OF INSECT ALLERGY AND ITS BEARING AS AN ETIOLOGIC FACTOR IN PAPULAR URTICARIA

It is well known, as is the case with most allergens, that newborn infants are not reactive to the intradermal injection of insect allergen.[21] (Table I) Also, the placement of insects on the skin of a newborn fails to give rise to either an urticarial or a delayed-type of response.[8] Similarly, an adult bitten for the first time by an insect to which he has never been exposed previously will show no reaction in the vast majority of cases, except possibly the appearance of a red punctum.[13] However, as the exposure is repeated, a delayed, tuberculin type reaction first appears. Further exposure will usually result in both immediate and delayed reactions at the bite site. With continued challenge, desensitization sets in, resulting in disappearance of the delayed reaction but with persistence of the urticarial phase. In some individuals, even the urticarial reaction eventually disappears.[13,15]

Thus it can be demonstrated that reactivity to insect bites involves many of the features of a true allergic reaction: namely, an initial incubation period, followed by a period of sensitization in which the delayed or tuberculin type reaction initially makes its appearance, to be supplemented later by the immediate type reaction. Desensitization with the disappearance of the late reaction often results from continued exposure, and finally, at times, even the disappearance of the early reaction has been noted. It is of interest to attempt an explanation of the clinical dynamics of papular urticaria on the basis of the above-allergic mechanism. In this connection, certain salient features of the disease should be emphasized:

1. *Papular urticaria rarely appears in the first year of life.* Newborn infants are not sensitive to most antigens and most certainly have had no exposure to insect bites. A period of refractoriness and an incubation period is needed, during which the child is repeatedly bitten and inoculated before sensitization is induced. The termination of the incubation period may not occur with the end of the first summer season, and during the ensuing winter the child is not likely to be exposed to insect bites. The first eliciting inoculation (bite) probably occurs with the beginning of the second summer season.

2. *The disease is found almost exclusively in hot weather months.* Insects, in general, are more active in summer than in winter. Fleas favor hot, humid climates. They are inactive in cold, dry weather. Bedbugs may persist throughout the winter, but in cold, underheated homes of the underprivileged, their activity is considerably diminished. Mosquitos are, of course, largely eliminated by cold weather. In climates where insects are perennial, papular urticaria is also perennial.

3. *After recurring for a number of hot weather seasons, the disease disappears spontaneously.* The characteristic lesions of papular urticaria are the wheal and the papule. The excoriative and impertiginous papules are merely modifications of these, induced by scratching. The essential lesion of papular urticaria, and the one without which the diagnosis cannot be made is the papule. The mechanism by which this papule develops can possibly be explained on the basis of the allergic features of insect bites. When the child begins to react to the bite of the insect, the late or tuberculin type reaction is first to appear. This corresponds to the papule clinically. Later, both urticarial and papular lesions are present, but in papular urticaria the papular lesions always dominate the clinical picture. When after many exposures, desensitization is finally induced (sometimes only after several summers) the papular phase disappears, and the patient is left only with the urticarial type lesions. These are transient and are readily recognized as insect bites. At this stage, he is said to be "cured" of his papular urticaria.

It would seem, then, that many cases of papular urticaria represent a transitional phase in the allergic cycle of some individuals to insect bites. Experimental evidence tends to substantiate this point of view. In our studies, most children beyond infancy, both patients with papular urticaria as well as controls, developed early immediate reactions to insect allergens, but the delayed type reaction was restricted almost exclusively to patients with papular urticaria. This means that most of these individuals, patients as well as controls, had been bitten by one or more of these insects (bedbugs, fleas, and mosquitoes), but that in patients with papular urticaria, desensitization to the delayed reaction had failed to occur.

Why do some individuals develop papular urticaria and not others? Most individuals will not develop papular urticaria, because (1) they are not exposed to bites, (2) the exposure is transient, light, and temporary, (3) the papular phase is evanescent, with rapidly developing desensitization (presumably the case with most individuals), (4) sensitization never develops, or, lastly, (5) these people do not attract these insects or may even actively repel them.[15] It is seldom that we see more than one child in a family affected with papular urticaria. This, of course, is a common experience in allergic states where many are exposed to an allergen but few react.

SUMMARY AND CONCLUSIONS

Papular urticaria is a cutaneous syndrome, characterized by the development of wheals and papules on the exposed parts of the skin. It occurs predominantly in children between the ages of two and seven years. It appears almost exclusively in the hot weather and is apt to recur for several summers before disappearing spontaneously.

There is reason to believe, on the basis of clinical, epidemiologic, allergic,

histologic, and therapeutic evidence, that many cases of this disease are due to allergy to insect bites. The responsible insect will vary in different localities depending on the dominant biting insect present.

Most patients with papular urticaria will react with immediate and delayed positive reactions to the responsible insect allergen, while normal contrals will have a negative response or a positive reaction only to the thirty-minute reading.

Histologic examination of the lesions of papular urticaria, positive skin tests, and insect bites show a similarity providing the lesions are at the same stage of clinical development.

Treatment with DDT as a local application and as an insect spray will "cure" the vast majority of cases of papular urticaria.

It is probable that many cases of papular urticaria represent a phase in the developmental cycle of the individual to insect allergen. In the normal individual the "tuberculin" type sensitivity phase is transient and/or ill developed, but in papular urticaria this phase is prolonged and severe and dominates the clinical picture.

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University of Pennsylvania

CHLOROMYCETIN® AVAILABLE

It will be good news to members of the College who prescribe Chloromycetin® (chloramphenicol) that Dr. E. A. Sharp, Director of the Department of Clinical Investigation of Parke, Davis & Company, has announced the continued availability of this outstanding antibiotic that has an established position in the physician's armamentarium, on a world-wide basis. This announcement is timely and necessary since the manufacturers on July 7, 1952, supplemented by pronouncements in the JAMA (July 12 and 26, 1952) informed physicians that several types of blood disorders are associated with the use of Chloromycetin®.

Pursuant to these pronouncements members of the medical staff of Parke-Davis have reviewed jointly with officers of the Food and Drug Administration several hundred case records collected from large centers of population throughout the country. These data were subsequently reviewed by a committee appointed by the National Research Council which concluded, in general, that there is evidence that certain cases of blood dyscrasias have been associated with the use of Chloromycetin®, suggesting that a warning should be placed on labels, in literature and in advertising, and proposing that the drug is not to be used indiscriminately or for minor infections. The evidence indicates that when prolonged or intermittent therapy is used, adequate blood studies should be made.

In view of the fact that a review of the available records implicates other drugs, used alone as well as concurrently with Chloromycetin®, as causative factors of blood disorders, the committee commented that paucity of information on these other drugs suggests further investigation of their role in the causation of dyscrasias of the blood.

The manufacturers are in full agreement with these conclusions and have notified the medical profession that "aplastic anemic, thrombocytopenic purpura, thrombocytopenia, and pancytopenia may follow the use of Chloromycetin; hence the precaution of judicious use, alert observation of the patient and adequate blood studies will be emphasized in all communications to the medical profession."

They further state that "continuation studies, in the laboratory and in the clinic, are being supported and expanded since it is believed that a fundamental feature of hematopoiesis may be clarified. The progress of this research will be reported when, as, and if important observations become available."

On August 13 the government ordered the manufacturers to label Chloromycetin with the warning that "'indiscriminate' use for minor ailments such as colds and acne might cause fatal blood diseases."

"The food and drug administration said it has found no reason why the antibiotic should not 'continue to be available for careful use by the medical profession in those serious and sometimes fatal diseases in which its use is necessary.'

"It has been effective for patients suffering from typhoid fever, Rocky Mountain spotted fever, undulant fever and pneumonia.

"The order was based on investigation of 177 serious blood disorder cases known to have some connection with the use of chloromycetin. At least seventy-two of the cases resulted in death."

With over a million patients who have taken this drug with beneficial results, the manufacturers are to be congratulated for continuing to make this antibiotic available, and for the continuation studies in the laboratory and in the clinic in an effort to clarify a fundamental feature of hematopoiesis.

THE PLACE OF THE ALLERGIST IN MEDICAL EDUCATION AND PUBLIC WELFARE

HORACE S. BALDWIN, M.D.
New York, New York

UNTIL recently it would seem that allergists, preoccupied with their relations to one another, the varying and opposing theories and concepts within their own field and the search for new phenomena and investigation along the lines of their own interests, have failed to join together in presenting a program that would emphasize the importance of the allergic diseases to the whole structure of the disease problem as it relates to human welfare. It would seem important and timely that allergists should now begin to elaborate a definite program to emphasize to the medical profession and to the public at large, the importance of the allergic diseases to medical education and to the social-economic phases of our national life.

Last year was notable among allergists in that it witnessed the meeting of the First International Congress on Allergy in Zurich. An important part of the program was devoted to papers which described the wide range of hypersensitivity reactions to disease in general. Thus, Rich[7] divided the diseases in which hypersensitivity plays an important role into two categories: (1) the primarily allergic diseases in which the disease state is the result of hypersensitivity to agents that are not in themselves intrinsically harmful on usual contact, and in which, had hypersensitivity not developed, no significant lesions attributable to the agent could have occurred, and (2) the diseases accompanied by sensitization in which the body becomes sensitized and thereby more readily damaged as a result of contact with agents which in themselves and in the absence of hypersensitivity *ordinarily* produce injury. The primarily allergic diseases include the hypersensitive reactions to pollens, epidermals, dusts, foodstuffs and many industrial chemicals and drugs. The second category, i.e., the diseases accompanied by sensitization, comprises particularly the conditions caused by micro-organisms, viruses, and parasites, in which sensitization to products of the invader renders the tissue more susceptible to injury by those products. The wide range of diseases that these types of hypersensitivity may cause include not only allergic rhinitis, asthma, eczema, and urticaria, but an extraordinary variety of visceral lesions including pneumonitis, myocarditis, focal necrosis of the lymph nodes and spleen, the formation of tuberculoid granulomata in the viscera, purpura, arthritis, periarteritis nodosa, neuritis, and glomerular nephritis. Rich further states that the "collagen-vascular diseases," which include particularly rheumatic fever, rheumatoid arthritis, periarteritis nodosa, and disseminated lupus erythematosus, constitute a highly important group of diseases charac-

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terized by focal collagen and vascular lesions of a type that strongly suggests that hypersensitivity may play a role in their pathogenesis.

At the same congress a very important paper on the social importance of the allergic diseases in England and Wales was presented by Dr. Williams of Cardiff.[9] His figures taken from the Registrar General's Report for England and Wales show that in the eleven years from 1938 to 1949, 23,067 deaths were attributed to asthma, or just under 3,000 per year. Asthma as a cause of wastage from the British Armed Forces 1943-1945 was seventh in order of importance; and as a cause of rejection of entrants to the Armed Forces, asthma ranked eighth in importance and accounted for nine per 1,000 rejections. Dr. Williams emphasized that of greater importance than the prevalence rate is the extent to which a disease causes incapacity. On this basis, in England and Wales, asthma ranks eighth in order of importance and is almost as common a cause of disability as gastric and duodenal ulcer combined, commoner than all fractures, than high blood pressure, angina and valvular heart disease combined, and causes practically twice the incapacity caused by all forms of tuberculosis.

What is the situation here in the United States? So far as our civilian population is concerned, an estimate by the United States Public Health Service[6] indicates that in 1948, 3,900,000 individuals suffered from hay fever and asthma and ranked the prevalence of these diseases third in a tabulation of chronic disease, following diseases of the heart and circulation, which lead the list, and arthritis and rheumatism, which are second. So far as mortality is concerned, figures[4] by Dr. Louis I. Dublin and Mr. Herbert H. Marks, statisticians of the Metropolitan Life Insurance Company, indicate that at least 9,000 persons with bronchial asthma die in this country every year and in the year 1940 asthma was the primary cause of death in 2,233 cases.

When it comes to our military personnel, it is challenging to note that in World War I, 7,797 patients with bronchial asthma were admitted to U. S. Army Hospitals, about two per thousand, or almost three times the number entered for peptic ulcer. Over thirty years later 3,322 veterans of that war whose asthma was service-connected were on the compensation rolls, and 1,800 others became totally incapacitated from the disease in the interim and received pensions. As of June 30, 1949, 36,541 veterans of World War II (all services) were on compensation rolls for asthma. Kern[5] further states, "In addition to these asthmatics, the veterans on the compensation and the pension rolls include 30,167 with the diagnosis of bronchitis; 6,460 with migraine; 786 cases of angioneurotic edema; 10,393 with chronic eczema; and 2,533 cases of exfoliative dermatitis. If the objection is raised that not all the cases of bronchitis, bronchiectasis, and migraine are allergic, it is pointed out that there are included no cases of gastrointestinal allergy, Ménière's syndrome, nor any in which an allergic disease might be a secondary diagnosis yet contributing to the patient's disability. The figures for allergic diseases above mentioned add up to

99,456, or 4.42 per cent of all veterans on compensation or pension. If we consider that the cost of all veterans' compensation and pension is now over two billion dollars a year, then the allergics' share is an important item in terms of taxpayers' money."

In *industry* the problem of hypersensitivity as applied to workers in the plants and the users of various products is becoming increasingly important. Synthetic fibers, synthetic fabrics, fabric finishes, dyes, ammunition, fertilizers, insecticides, cosmetics are only a few of the general compounds of modern industrial chemistry which may cause important allergic disease.

The mounting importance of hypersensitivity reactions to our modern drugs is evident to us all. The hazard attached to the tremendous use of the antibiotics and the development of hypersensitivity to these drugs as time goes on is part of this serious problem.

* * *

Up to this point I have attempted to describe the wide prevalence of allergic disease and its importance in our modern civilian, military, and industrial life. In the attack on allergic disease the co-operation of medical education is fundamental. Here it is evident that so far as the allergic diseases are concerned medical education is not measuring up to the great demand that is necessary.

In medical education at the undergraduate level, it is probable that our courses in medical schools underemphasize the importance of allergic diseases.[8] Barr[2] states, "it is more than deplorable that many young internists have been permitted to finish their training without contact with allergy and allergic thought." Certification in internal medicine and pediatrics is often allowed with no knowledge of the candidate's qualifications for diagnosis and treatment of these diseases. When it comes to the training of residents and fellows in allergy, there are just thirteen institutions in the U. S. approved by the Council on Medical Education of the A.M.A. for this purpose, and a not infrequent complaint of the men in charge of these projects is that they have great difficulty in attracting high grade men to fill these positions.[1]

It is obvious that we as allergists have a tremendous responsibility to provide leadership. What specifically can we do?

First, it seems to me that each one of us needs to catch the vision of the broad field we are engaged in without neglecting our own special techniques and diagnostic aids. We must continue to emphasize the importance of hypersensitivity factors as demonstrable by the skin test, the importance of reliable extracts, and experience in the techniques of testing. But further than this we should recognize the importance of infection, of irreversible structural damage, of psychosomatic factors. We should realize that there are many gaps in our knowledge that only future research and investigation may close. We should be familiar with the broadening concept of hypersensitivity to include the collagen-vascular diseases and be

concerned with the serious lesions which may result from hypersensitivity to sensitizing drugs, the list of which is already large and rapidly increasing.

* * *

In the field of medical education, allergists should present a united front and a united program. At the same time it is important for us to realize that not all the fault for inadequate teaching of allergy in medical schools and hospitals can be blamed on our professors of medicine. The fact is that in many of our medical schools there has been no one on the staff adequately trained to integrate the subject of the allergic diseases with basic immunological knowledge and clinical medicine.[3]

When we come to our social responsibility, there are several objectives which we need to attain.

First, the general public has failed to grasp the serious significance of hay fever, bronchial asthma, and eczema as causes of chronic disease and disability. Nor has the general public much idea of the broader concepts of allergy and its relation to drug reactions, the various manifestations of collagen disease, bacterial infection, and psychosomatic medicine. It is obvious that there is a real need for better dissemination to the public of information which will give the real facts about allergic disease and proper methods of diagnosis and treatment.

Second, allergists have suffered from lack of funds to establish fellowships and support investigation in our medical schools and research centers. This does not imply that a great deal of very valuable work has not been done. Yet there are many problems still unsolved which we as allergists are particularly interested in approaching through our own experience and under our own direction and orientation for which money should be available.

Third, we have an important duty to train young men in the diagnosis and treatment of allergic disease. Residencies for the training of allergists are few and far between. Money is needed to establish them, and at the same time standards for residency training in allergy need better formulation. If we are to improve undergraduate teaching in our medical schools, we must train young men properly at the resident level in allergic disease with a broad base of experience in the fundamental sciences and clinical medicine. Men so trained will make good teachers and will influence better understanding of the allergic diseases in our future physicians graduating from medical school.

Fourth, proper care and rehabilitation of the patient with allergic disease in our lower economic group is often unobtainable. Organized philanthropy, so well carried out by the American Heart Association, the National Tuberculosis Association, the National Foundation for Poliomyelitis, the American Cancer Society, does not exist for the disabled asthmatic patient. As allergists we have an obligation to these people to dramatize their problem and raise money for their proper care.

Last February in Chicago, the American Academy of Allergy held its

annual meeting in an atmosphere characterized by a constructive spirit of unity among allergists. The American College of Allergists is characterized by the same spirit. Last year in Zurich, the two great American allergy groups got together and joined with other national societies to form an international association of allergy under the presidency of its founder (as well as the founder of the College), Fred Wittich. It would seem that at the present time our two allergy societies are willing to join hands in trying to solve the problems of allergy as they relate to medical education and public welfare. Two allergy societies co-operating may well be more forceful than one large combination. Many of you are aware that The American Academy of Allergy has sponsored the organization of a Foundation for the Allergic Diseases. The medical trustees as originally selected include not only men interested in the Academy but also men whose interests have been primarily in the College. As set up, the Foundation will be divorced (in a friendly fashion, we hope) from the Academy. It is not to be the creature of any organization. It has been sponsored by the Academy as the International Association of Allergology has been sponsored by the College. But in its eventual organization it will not be managed by either society. At present the Board of Trustees has authorized an investigation of fund raising and public relations firms with the idea of having the best organization make a survey of the possibilities of enlisting widespread lay support in a campaign to raise money for the purposes of the Foundation. These include better public relations about the allergic diseases, better treatment for the allergic patient, the establishment of residencies and fellowships in allergy, and investigation into the problem of the allergic diseases. Lay trustees will have to be selected. A scientific and educational council must be set up. Local groups will have to be formed. A tremendous amount of spade work will have to be done before the first dollar is raised. But as time goes on, if we will work together we should have an organization which will present a program for the improvement of allergy in medical education, practice, and research. It offers a challenge to every allergist to get behind and push for its success and for the two national allergy societies to work together in a common worthwhile cause.

SUMMARY AND CONCLUSIONS

1. The wide range of hypersensitivity reactions in disease is described not only to include hay fever, bronchial asthma, urticaria, and dermatitis, but also to stress the importance of hypersensitivity in drug reactions, industrial chemistry, and the whole group of collagen diseases.

2. Morbidity statistics indicate that there are at least 3,900,000 persons in the United States who suffer from hay fever and asthma, ranking this category of chronic disease third in prevalence following diseases of the heart and circulation—and arthritis and rheumatism.

3. In connection with the military services, statistics as of June 30,

1949, indicate that 36,541 veterans of World War II were on compensation rolls for asthma, and the sum total of all veterans on compensation or pension rolls because of some allergic disease may amount to nearly 100,000.

4. Medical education in allergic diseases at the undergraduate and graduate levels is inadequate to provide for the training of young men fitted for practice, teaching, and research in this specialty.

5. The formation of the Foundation for the Allergic Diseases offers the possibility of providing better education of public and physicians in the proper treatment and management of allergic disease, financial support for the training of younger physicians in practice, teaching and research in the allergic diseases, funds for research, and rehabilitation of sufferers from allergic disease in the lower economic group.

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136 E. 64th Street

TWO FEATURE ARTICLES IN SEPTEMBER QUARTERLY REVIEW OF ALLERGY AND APPLIED IMMUNOLOGY

Attention is called to two special articles which will appear in the September issue of the *Quarterly Review of Allergy and Applied Immunology*, along with the extensive review of the literature on allergy and applied immunology and Dr. Jonathan Forman's expanded bibliography.

The first paper, entitled "Repository Histamine Therapy in Allergy," is a presentation by Dr. Hinton D. Jonez, Multiple Sclerosis Clinic, St. Joseph Hospital, Tacoma, Washington, who has had much practical experience with the use of histamine. The article is published to present evidence in favor of the use of histamine in the treatment of certain allergic conditions.

The second paper, entitled "Chemical and Immunological Properties of Timothy Grass Pollen Extracts and Problems of Standardization," is written by R. Augustin Friedmann of The Wright-Fleming Institute of Microbiology, St. Mary's Hospital Medical School, London, England. This is a critical review of the previous methods of standardization of pollens, with a refreshing new approach to the problem by a brilliant investigator who has devoted much of her time to the subject. There is still much to be learned about the method of purification and standardization of pollen antigens. No allergist should miss this treat!

NITROGEN MUSTARD IN THE TREATMENT OF BRONCHIAL ASTHMA

GEORGE L. WALDBOTT, M.D., F.A.C.A.
Detroit, Michigan

JIMENEZ-DIAZ et al[6] reported remarkable improvement in rheumatoid arthritis from intravenous injections of nitrogen mustard. Their results, they felt, paralleled in many respects those obtained from cortisone and ACTH. Following up these observations on rheumatoid arthritis, they administered nitrogen mustard to eighteen asthmatic patients, of whom all but two obtained considerable relief. I accumulated certain data on this method of treatment following a visit in Madrid, where I observed some of their cases. This report is concerned with the clinical results in twenty-one cases of asthma and four of chronic atopic eczema.

RATIONALE

Several observations suggest a theoretical basis for a therapeutic trial of nitrogen mustard (HN_2) in asthma: According to Hektoen and Corper[5] there is a reduction in antibody formation in animals treated with sulfur mustard. The Schwartzman reaction in rabbits is suppressed (Becker[1]) in animals pretreated with HN_2. There is known to be a moderate leukopenia and a definite decrease of lymphocytes after administration of HN_2. Enlargement of lymphoid tissue is a common feature in asthma, especially in incipient cases (Waldbott[8]). Destruction of lymphocytes is known to play a part in the liberation of antibodies.[7] Finally, in the use of HN_2 various features resembling the mode of action of ACTH and cortisone have been noted, such as reduction of eosinophiles, increase of 17-ketosteroids in the urine and adrenal hyperplasia.[2]

METHOD

All patients selected for this series had been under treatment for asthma for several months or years. They were chosen from a larger group of chronic cases because their disease had been unusually intractable. All patients had had symptomatic treatment as well as eliminative procedures and hyposensitization treatment. The majority had one or more courses of cortisone, ACTH, or both; they had been hospitalized on several occasions.

The technique of the treatment was that usually employed for malignant diseases. The patients received 1/10 mg of Mustardol (Merck) per kg of body weight intravenously for four successive days. In order to counteract the unpleasant side effects, they were given Dramamine, 50 mg one hour previous to, and another dose at the time of, administration

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of the mustard. They also received 1 cc of Hexavibex, which is said to be effective for this purpose.*

RESULTS

Table I presents the results obtained. We were mainly interested in terminating the asthmatic state and less concerned with observing any permanent effect. The time of observation is therefore limited, as indicated in column 4. All patients, with the exception of three, were considerably relieved for a period of one to seven weeks. It is true that some have remained free from symptoms since the treatment was given; however, one would expect spontaneous remissions of long duration in an average group of asthmatic individuals, once the asthmatic state had been brought under control. Indeed, in by far the majority of cases (column 6) the attacks recurred within a few weeks. The cessation of attacks usually occurred after the second or third treatment. After the fourth dose the attacks, no matter how severe, were usually under control. The two asthmatic patients in whom no benefit whatsoever was noted improved following bronchoscopic lavage, which yielded large quantities of thick mucous plugs. There were four individuals in this group with atopic eczema, one of whom was a particularly intractable case. They showed a marked improvement and subsequently cleared up by other means.

There were marked side effects (column 5), especially nausea, vomiting, anorexia, and in two cases, diarrhea. Vomiting was so severe in three cases that the four injections which had been planned could not be given. While these symptoms usually subsided within eight to ten hours, two individuals complained of nausea and dizziness for about a week. Seven patients experienced no ill effect with the exception of slight nausea. We observed a depression of the eosinophil count and the white blood count which lasted for one to two weeks. In three cases there was a considerable decrease in the amount of sputum. Two patients exhibited a marked reduction in the reactivity of the skin upon intradermal testing about one week after the treatment. No evidence of anemia or hemorrhagic disease was encountered in our cases.

DISCUSSION

In evaluating these results, a definite parallelism of the action of mustard with that of ACTH and cortisone is evident: the benefit derived from these therapeutic agents is only temporary. Improvement becomes noticeable after the second or third dose and is very definite after the fourth day. The marked drop in eosinophilia which was noted on several patients suggests a pituitary-adrenal effect of HN_2. An increase in the urinary excretion of 17-ketosteroids was also noted by Jimenez-Diaz.

The possibility must be considered that a psychosomatic effect could

*I appreciate the valuable advice of Dr. Dan Meyers, Chief of Medicine, Grace Hospital, in working out the technique of this treatment.

TABLE 1.—MUSTARDOL TREATMENT IN 21 CASES OF BRONCHIAL ASTHMA AND 4 OF ATOPIC ECZEMA

I Case			II	III Present Asthmatic State		IV Treatments			V Vomiting	VI Improvement	
No.	Name	Age	Type of Asthma*	Duration	Severity	Date 1952	Dose mg.	Number	Degree	Degree	Duration
1	R.P.	64	Advanced emphysema. Cystic degeneration of lungs	Constantly for 3 years	+++	1-17	5.8	4	++	0	
2	A.S.	55	Very persistent. Uncomplicated	6 months	+++	1-19	5	4	+++	+++	Free from symptoms since treatment
3	P.F.	73	Very constant. Formerly evidence of Loeffler's syndrome	3 months	+++	1-25	6.5	4	++	0	
4	E.M.	26	Moderately severe	3 months	++	2-4	8	4	+++	+++	Free from symptoms
5	B.M.	20	Advanced—very chronic	4 months	+++	2-6	5	4	+	+++	Free from symptoms since
6	W.C.	56	Extremely chronic and severe, but no permanent lung pathology	6 months	+++	2-9	7	4	0	+++	6 weeks
7	C.C.	56	Influenced by psychosomatic factors	4 months	++	2-14	2 5 10 5	4	+++	++	4 weeks
8	L.B.	49	Moderately severe, very chronic, coincident with chronic myocarditis	7 months	+++	2-21	4.5	4	++	+	10 days
9	T.T.	26	Moderately advanced; extreme degree of emphysema	5 months	+++	3-1	5	4	++	+++	7 weeks
10	H.W.	39	Aggravated by, but not relieved by elimination of, occupational dust	5 months	++	3-2	9	4	+	++	Until return to work—3 weeks
11	E.G.	37	Very chronic, moderately severe	4 months	+++	3-11	4.8	4	+	+++	2 weeks. Had severe hives 4 to 7 days later
12	J.R.	30	Very chronic and refractory to treatment	4 months	+++	3-12	6	4	+++	+++	3 weeks
13	M.C.	63	Chronic, but intermittent attacks	2 months	+	3-17	6	4	0	+++	Still free
14	E.K.	40	Moderately severe, intermittent	2 months	++	3-13	5	4	0	+++	Free
15	A.P.	62	Chronic, uncomplicated	3 months	+++	3-17	5	4	++	++	5 weeks
16	P.B.	45	Chronic state with very severe exacerbations	1½ months	+++	3-22	5	4	0	+++	2 weeks
17	H.S.	43	Extremely severe attacks intermittently	3 weeks	+++	3-31	8	1	Extreme	+	Had to discontinue treatment
18	R.C.	44	Chronic, moderately severe	4 months	++	4-2	7.8	3	+++	+	1 week
19	A.D.	60	Constant attacks	2 months	+++	4-16	7	4	0	+++	
20	A.G.	56	Moderately severe, constant wheezing	3 months	++	4-21	7	4	++	++	
21	E.P.	19	Very chronic and severe	3 months	+++	4-12	7	7	+	+++	1 week
			Eczema								
22	E.C.	21	Severe atopic eczema	1 month	+++	4-12	7	4	0	++	3 weeks
23	G.K.	34	Very chronic, moderately severe	3 months	++	4-15	5	4	0	+	1 week
24	A.B.	20	Atopic eczema aggravated by contact factors	3 months	++	4-18	6	3	+++	0	
25	H.S.	40	Constant	20 years	+	4-12	7	4		+++	4 weeks

*All cases were allergic; average duration 6.2 years.
0—None
+—Little
++—Much
+++—Very Much

have accounted for the improvement with a therapeutic procedure, the side effect of which must necessarily be very impressive to a patient. This can be ruled out in our cases, since all had had numerous other methods of treatment and had been under extensive observation. The only individual (Case 7) in whom a psychosomatic effect was considered because of her general make-up did not obtain favorable results.

Twelve patients in this series had had intravenous injections of either typhoid vaccine or pyromen on previous occasions. According to our observations, and to the patients' own judgment, improvement following these injections was not as impressive as that following mustard therapy. Indeed the only other therapeutic agents with which this treatment can be compared are cortisone and ACTH.

There are definite disadvantages connected with this mode of therapy. The severe nausea and vomiting which are common makes HN_2 undesirable if compared with cortisone and ACTH. On the other hand, in cases in which these two drugs cannot be administered because of their well-known side effects, e.g., in hypertension, diabetes, and various types of infections, HN_2 may be the method of choice. Jimenez-Diaz has administered several courses of HN_2 treatment. I hesitated to give a second course because it has to be given intravenously; without the possibility of doing a skin test with as irritating a substance as HN_2, there is no way of definitely avoiding anaphylactic shock; sensitivity to this substance might conceivably be acquired by the first course of treatment. One might consider administering HN_2 at two- to five-day intervals for a longer period of time.

Pregnancy constitutes a contraindication because deformities have been observed in the offspring of animals treated with mustard (Haskins[4]). In patients with a tendency to hemorrhagic diathesis or leukopenia, the drug should not be employed because toxic doses of HN_2 are likely to aggravate these conditions.

SUMMARY

Twenty-one patients with severe, "intractable" allergic asthma and four with chronic atopic eczema were treated with injections of Mustardol (Merck). All but four of the conditions improved temporarily following this treatment. In many respects the effect of this drug parallels that of cortisone and ACTH. Among unpleasant side effects, severe vomiting was encountered, which necessarily limited its administration.

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602 Professional Building

NINTH ANNUAL CONGRESS

(Including Graduate Instructional Course)
April 24-29, 1953

Dr. Giles A. Koelsche, Mayo Clinic, over-all chairman of the Graduate Instructional course of the Ninth Annual Congress of the College to be held at the Conrad Hilton Hotel next spring, is making elaborate plans for an outstanding scientific program, with the able assistance of Dr. Morris Kaplan, Chicago, and Dr. Leon Unger, Chicago, as co-chairmen.

Arrangements are being made by the Local Committee and the Ladies' Auxiliary for a varied and interesting entertainment program for all.

Practically all of the exhibition booths have already been engaged. Quarters for the Congress are on the second floor of the hotel facing Lake Michigan. In due time members will be receiving from the Conrad Hilton Hotel a card quoting room rates which should be filled out promptly.

The First Congress of the College, held at the Palmer House in Chicago ten years ago, had a registration of 1,000. The weather in the latter part of April in Chicago is usually quite fair. Please make your plans now to attend. If you have a research project on investigative or clinical allergy try to have it completed by next February and submit it to Dr. Giles A. Koelsche, Department of Internal Medicine, Mayo Clinic. Excellent papers have already been submitted for approval. Let us make this beginning of the second decade of the College one which will be inspiring and exemplary for the annual meetings to follow.

CHICAGO SOCIETY OF ALLERGY

At the last meeting of the Chicago Society of Allergy the following officers were elected for the year 1952-53:

President—Milton M. Mosko, M.D., Chicago, Illinois

President-Elect—Abe L. Aaronson, M.D., Chicago, Illinois

Secretary-Treasurer—Simon S. Rubin, M.D., Gary, Indiana

Committee appointments of the Chicago Society of Allergy are as follows:

Executive Committee—Milton M. Mosko, Morris A. Kaplan, Townsend B. Friedman, Theron G. Randolph, Simon S. Rubin

Program Committee—Max Samter, Chairman; Samuel M. Feinberg, Townsend B. Friedman, Samuel J. Taub

Public Relations Committee—Harry L. Huber, Chairman; Ben Z. Rappaport

SOY BEAN MILK AS A SUBSTITUTE FOR MAMMALIAN MILK IN EARLY INFANCY

With Special Reference to Prevention of Allergy to Cow's Milk

JEROME GLASER, M.D., F.A.C.A., and DOUGLAS E. JOHNSTONE, M.D.
Rochester, New York

ALTHOUGH it has been shown[13,19] that unaltered proteins pass the intestinal barrier and may enter the blood stream under normal physiological conditions at all age periods, it is a common observation among pediatricians and allergists that food sensitivities are much more frequent in the first few months of life than in later childhood and adult life. It is assumed that physiologic immunological immaturity exists in the earliest months of life, which results in clinical symptoms from absorption of unaltered proteins in allergenically predisposed children. These same symptoms, of which atopic dermatitis and allergic gastrointestinal disorders are the most frequent and distressing, do not necessarily occur in the same child when he absorbs the same unaltered protein toward the end of the first year. This phenomenon, with particular regard to the intolerance of many children to egg yolk under the ages of six to nine months, observed by Glaser* in the late nineteen twenties, was the starting point of this present study. The authors postulated that if the protein which constitutes the chief source of food and is most commonly the cause of a multiude of clinical allergic phenomena (i.e., cow's milk) were withheld completely from the infant's diet until this period of physiologic immunological immaturity were passed, the symptoms of milk allergy might be avoided, minimized, or even prevented. Consequently, the incidence of atopic dermatitis (eczema) and intestinal intolerance to cow's milk, which comprise two of the most exasperating syndromes facing pediatricians and allergists, might be reduced.

It was the purpose of this study to determine (1) the possibility of successfully nourishing infants with a vegetable protein substituted for mammalian milk from the time of birth, (2) the incidence of intolerance and sensitivity to this substitute in the early months of life, (3) the incidence of general allergic phenomena in infants while on this test diet, and (4) the incidence of intolerance to cow's milk at the time these infants' formulae were finally changed to cow's milk. The subsequent follow-up of these children, compared to a control series with reference to the subsequent de-

From the Department of Pediatrics of the University of Rochester School of Medicine and Dentistry, the Genesee Hospital, and the Strong Memorial Hospital, Rochester, New York.

Presented at the Eighth Annual Congress of The American College of Allergists, April 7-9, 1952, Pittsburgh, Pennsylvania.

This work was done as part of the requirements for the Fellowship in Pediatric Allergy held by Dr. Johnstone.

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*Unpublished data.

velopment of allergic diseases, will form the basis of a future communication.

METHODS

Beginning in 1942, the reasons for this study were explained to parents, one or both of whom were allergic, or who had at least one allergic child, and who were expecting the arrival of another infant who would be under our care. The expectant mother was placed on a diet designed to prevent excessive ingestion of antigens which might sensitize the infant *in utero*. If she chose to nurse her baby subsequently, the diet was continued. At birth, the infant was placed on soy bean milk either as the sole source of food or as a complementary feeding. As long as she nursed her child even once daily, she was encouraged to continue eating this special diet low in egg and milk, as previously described by Glaser.[8] Sixty-seven infants were started on this regimen. Two infants, by error, were given a single feeding of cow's milk. The milk substitute used in this study was a proprietary soy bean preparation, Mull-Soy.* The starting formula was usually one third Mull-Soy and two thirds water, which was gradually increased, as tolerated, to a formula of equal parts of Mull-Soy and water. The hospital nursery record of every child was reviewed for notes concerning intestinal disorders or possible evidence of intolerance to soy bean milk. Each baby was examined and re-evaluated approximately monthly during the first year. The record of each child was carefully reviewed for signs of intolerance to soy bean milk or any other allergic phenomena during the period the soy bean milk was given and following the final introduction of cow's milk to the diet. The weight of each infant at the time soy bean milk was discontinued, as well as at the age of one year, was compared with the weights for the norms of comparable age and birth. The length of time these infants were kept on formulae of soy bean milk before being switched to cow's milk feedings is noted in Table I.

TABLE I.

Age When Taken Off Mull-Soy	Number of Infants
Less than 1 month	5
1-3 months	13
3-5 months	7
5-9 months	42

RESULTS

At the time the infants in this study were taken off soy bean milk, fourteen weighed less and twenty-eight weighed more than their expected weights for their ages and birth weights. Of the twenty-nine infants who were followed over one year, the weights of twenty-four of them exceeded their expected weights at one year of age. There were no clinically detectable differences in dentition, activity, behavior, intelligence, or other

*Manufactured by the Borden Company, New York, New York.

physical attributes between these children and infants of comparable age and social and economic backgrounds in our practice.

Of the sixty-seven infants, nine (13.5 per cent) were thought to be intolerant to soy bean milk during the neonatal period. The symptoms necessitating the discontinuance of soy bean milk in these nine infants are noted in Table II. One other child had diarrhea and emesis not relieved by changing to cow's milk or other formulae, so that he was not considered truly specifically intolerant to soy bean milk, although this possibility cannot be ruled out. He made a very gradual recovery.

TABLE II. CONDITIONS NECESSITATING DISCONTINUANCE OF THE SOY BEAN MILK

Persistent diarrhea	in 2 infants
Emesis	in 2 infants
Colic	in 2 infants
Diarrhea and emesis	in 2 infants
Diarrhea, emesis, and atopic dermatitis	in 1 infant

Just why some infants are unable to tolerate soy bean milk we are unable to state. We are reluctant to attribute this to allergy in the absence of studies which might tend to confirm such an opinion. It is our impression that some infants are unable to tolerate a vegetable milk with its relatively large, bulky stools without disagreement manifested by either diarrhea or vomiting. We feel that this intolerance is probably dependent upon physiological and anatomical immaturity of the intestinal tract, rather than on allergy to soy bean milk, although it is evident that such allergy has not been ruled out.

Eleven infants at some time had emesis while on soy bean milk. Of these, only five, listed above, did not respond to customary medication and required discontinuance of the soy bean milk. A sixth developed hypertrophic pyloric stenosis at the age of five weeks, after having been on soy bean milk feedings since birth. Following operation, he was put on cow's milk and did well. It is within the realm of possibility that the spasm and subsequent hypertrophy of the pyloric musculature was due to sensitivity to soy bean, but this cannot be proven.

Twenty-two infants had varying degrees of diarrhea while on Mull-Soy. In no instance was the diarrhea thought to be of infectious origin. Thirteen of these infants responded to symptomatic medication with Kaopectate.* Usually one teaspoonful in each bottle of Mull-Soy sufficed. Four did well on paregoric therapy. Only five did not respond to symptomatic medication and required discontinuance of the soy bean milk. These spontaneously improved when the Mull-Soy was stopped. Eleven infants had varying degrees of colic but in only two were these of sufficient mag-

*Manufactured by the Upjohn Co., Kalamazoo, Michigan.

nitude to require discontinuance of the soy bean milk.

Three infants developed atopic dermatitis while on the soy bean milk, but only one case was severe and suspected of representing a true intolerance to Mull-Soy. Unfortunately, we have been unable to follow this patient further. Two infants developed allergic phenomena due to ingestion of spinach while on the Mull-Soy formula. One of these had diarrhea and the other developed curcumoral dermatitis with each meal containing spinach. There were no other instances of definitely allergic phenomena in these sixty-seven infants while on the soy bean formulae.

Thirteen infants developed seborrheic dermatitis, which was more than a simple "cradle cap," while on the soy bean milk. It must be emphasized that seborrheic dermatitis is definitely not an allergic disease. None of these subsequently developed atopic dermatitis.

At the time these sixty-seven infants were first given cow's milk feedings, four children were thought to have some difficulty tolerating cow's milk formulae. One child, who was taken off Mull-Soy at eight months of age, developed mild looseness of his stools when changed to evaporated milk. A second child, taken off soy bean milk at five months, developed severe colic from evaporated milk and improved immediately on returning to Mull-Soy feedings. A third infant began to vomit when whole cow's milk was introduced at eight months. He improved when put on a goat's milk formula. At ten months he was able to tolerate homogenized whole cow's milk. While these cases must be considered as instances of congenital sensitivity to cow's milk, analogous to the much better known congenital sensitivity to egg, the possibility that these infants, during their hospital stay, may have received, by error, one or more unrecorded feedings of cow's milk formula cannot be excluded.

DISCUSSION

The earliest reference to the use of soy bean milk as a milk substitute in infant feeding is that of Ruhräh[15] in 1909, who did not use it alone but in combination with other foods.

In 1917 Osborne and Mendel[12] stated that the soy bean contains all the proteins necessary for normal growth of infants. Until it was known that a heat-labile trypsin inhibitor is present in large quantities in soy beans,[4,11] early physiologists and nutritionists were puzzled as to why this adequate protein failed to support adequate growth. However, modern methods of preparing soy bean flour inactivate this inhibitor. Tso,[17] in China, in 1929 successfully fed six infants for six to nine months, one from birth, on a diet in which soy bean was used instead of mammalian milk. Except for those cases briefly mentioned by Glaser[8] and included in this series, the report of Tso is the only recorded instance of an infant fed soy bean milk instead of animal milk from the time of birth. Albanese[1] in 1951 presented data to show that the amino-acid content of soy beans may actually be superior to the protein of breast milk in meeting the known

amino-acid requirements of infants after the first few weeks of life.

In a study of allergic children in an average older age group, Clein[5] found that 6 per cent of them were intolerant to soy bean milk. Our data suggest an incidence of intolerance of about twice that figure. This is doubtless due to the fact that our cases were started at birth and Clein's at an average age of several weeks or months. One factor which also influences the incidence of "intolerance" to Mull-Soy is the apprehension of many mothers, who always have some doubts about the validity of feeding a baby anything other than the orthodox cow's milk. In our work, this was particularly noted early in the study.

Before putting any infant on the soy bean feeding regimen, we always encouraged a trial of breast feeding. This was done because the studies of Grulee and Sanford[9] had clearly shown that the exclusively breast fed infant has seven times as many chances of escaping eczema as the bottle (cow's milk) fed infant. If she nursed her child, the mother was placed on a special diet low in egg and milk, as previously described by Glaser.[8] However, despite all encouragement from obstetrician, pediatrician and obstetrical nurses, the mothers of most of the babies in our series refused even to attempt breast feeding.

The fact that infants do absorb unaltered proteins from their intestinal tracts was most dramatically demonstrated by Walzer,[18] who stated: "We tried feeding egg white antigen, mixed with formula, to newborn infants who had been passively locally sensitized, and found that a positive reaction developed before they had finished their bottles. The gastrointestinal tract of the newborn infant is almost like a sieve." This fact had been substantiated by the use of precipitin studies by Ganghofner and Langer[7] and by Schloss and Anderson.[2,3,16] This phenomenon has been shown, not only for milk, but also for wheat and egg-white proteins which are frequently the sources of distressing allergic phenomena in infancy. Consequently, we feel that these foods should be withheld from infants' diets until after the period of immunological immaturity has been passed. From Glaser's* observations on egg yolk, this period is presumed to be a minimum of six to nine months. The authors believe that egg should be withheld at least one year in children of known allergic hereditary background. The infant should then be started gradually on hard boiled egg yolk, with hard boiled egg white and then whole egg in other forms gradually introduced into the diet as tolerated. From an immunological standpoint, egg yolk may be considered a highly diluted form of egg white, and it is the egg white protein in the yolk which is responsible for the allergic reaction. Egg yolk is said to contain a specific protein of its own,[6] but, thus far, no infant and only one adult[14] has been proved specifically sensitive to egg yolk. It should be further pointed out that all reactions to egg white cannot be avoided by hard boiling, since the ovomucoid of egg

*Unpublished data.

white is not rendered insoluble or altered immunologically by boiling.[10]

Based on the same general reasoning for starting potentially allergic infants on soy bean milk instead of cow's milk to avoid sensitizing the infant to cow's milk, we feel that it is unwise to start these infants on such an important food as wheat for the first cereal. We prefer to start the infant on barley or oat so that, if the acquisition of sensitivity in such infants, which to a certain extent appears to be a function of age, does occur, the infant may be changed to wheat cereal at a later date with less danger of being sensitized. This indicates, of course, the use of single cereals instead of the presently more popular multiple cereals. Acquired sensitivity to fruits, vegetables and meats occurs much less frequently. Here variety should be used. The potentially allergic infant should not, for example, be fed orange juice daily, but a variety of juices, the ascorbic acid deficiency of some of these, when necessary, being compensated for by adding ascorbic acid to the juice.

SUMMARY AND CONCLUSIONS

1. Our own observations and evidence obtained from the literature indicate that the gastrointestinal tract of the newborn is highly permeable to unaltered proteins. It seems fair to assume that this is associated with immunological immaturity of physiological origin.

2. It also seems fair to assume that, if the foregoing statement is true, the potentially allergic newborn child (i.e., the child of parents one or both of whom are allergic or who have had a previous child who is allergic) is more likely than a newborn who is not potentially allergic in the sense just mentioned, to become sensitized to the first foods which pass the gastrointestinal barrier.

3. This being the case, it would seem logical to start a newborn infant on a food of adequate nutritional value but of such a nature that, if the infant became sensitized to it, even permanently, this would not present a problem of any significance in later life because of adequate and acceptable substitutes for this food.

4. It has been shown that a preparation of soy bean milk (Mull-Soy) may be used successfully in over 85 per cent of cases to feed infants from birth, and that these infants may later be changed over to cow's milk formulae without difficulty except in those cases where there is probably a persistent congenital sensitivity to cow's milk.

5. This is the first series to be reported of infants successfully fed from birth on a substitute for animal milk, except for a single case reported by Tso[17] in 1929. The average infant so fed did better, when compared to accepted standards for the normal development, than infants fed on the breast or on orthodox cow's milk formulae. There were no other observable differences, in any way, between the two groups of infants.

6. If the observations and conclusions expressed above are correct, then it is possible to introduce a new basic principle into infant feeding.

This consists of feeding with respect to improving the *immunological status* of the child with respect to food allergy as compared with the present practice, which is to feed the child so that he will grow and develop according to accepted standards of *physical normality*. Our work indicates that these two principles may be applied simultaneously.

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THE PHYSICIAN'S RESPONSIBILITIES

"The medical profession has a responsibility, not only for the cure of the sick and for the prevention of disease, but for the advancement of knowledge, upon which both depend. This third responsibility can be met only by investigation and experiment."—McCance, R. A.: Practice of experimental medicine. Proc. Roy. Soc. Med., 44:189-194, 1951.

HORMONAL-CONNECTIVE TISSUE MECHANISM IN ALLERGY

AUBREY G. RAWLINS, M.D., F.A.C.A.
San Francisco, California

WHILE the immunological antigen-antibody mechanism in allergy explains many things, it does not account for all allergic reactions; and, in many allergic patients, sensitizing antibodies cannot be found either in the tissues or in the blood stream. Also, therapy along this line, while effective in many cases, still falls short in others.

Williams[10] has proposed the hypothesis that, fundamentally, allergy is a localized autonomic dysfunction associated with arteriolar spasm, anoxia, increased capillary permeability, and hence edema in the tissues. Hilger[5] has supported this idea and also has brought out the fact that the autonomic dysfunction is an inherited trait in allergic individuals. This hypothesis gives a much broader base for the allergic picture. There is good microscopic *in vivo* evidence to support it, and I am in full agreement with it. The hypothesis gives a reasonable explanation for the allergic patients with so-called physical allergy.[12] These patients react allergically to stress of almost any kind. For example, emotional strain, overwork, dampness, excessive cold, changes in barometric pressure, et cetera, all produce the same symptoms in many allergic individuals as does contact with an allergen to which they are sensitive. Also, this hypothesis adds to the therapeutic possibilities in allergy. The main addition in therapy is the use of vasodilators to overcome the arteriolar spasm as well as other methods to decrease capillary permeability.

In spite of this added information the therapeutics of allergy fall short of our aim. Hence we might pause and ask ourselves: is there anything that universally aids all types of allergic reactions? If so, from this starting point, it should be possible to develop a sound hypothesis for the basic mechanism of allergic pathology.

ACTH and cortisone therapy come so close to fulfilling the answer to this question that pure logic would indicate that the study of the action of these hormones should eventually give us the solution to the fundamental allergic mechanism. In order to do this, we must go back to the ground substance of primitive mesenchyme.* While this is one of the oldest known structures in the body, it is only of recent date that it has developed a personality of its own. Connective tissue comes from the primitive mesenchyme, which is a mass of firm amorphous gel containing a few cells and fibrils. This amorphous substance or gel is composed mostly of mucopolysaccharides.[2] The most important of these is hyaluronic acid.

From the Department of Otolaryngology, Stanford University School of Medicine.
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*The terms *ground substance, amorphous substance, hyaluronic acid, mucopolysaccharides,* and *gel* will be used interchangeably in this article.

The term *cortisone* has been used rather loosely in this article. Actually ACTH probably stimulates the adrenals to produce more Compound F than cortisone. However, the physiologic action of the two is similar.

As the connective tissue develops, fibroblasts multiply in the gel, and fibroblastic fibrils form into bundles of collagen fibers. Some become coated to form elastic fibers.

The peripheral vascular bed with its arterioles, capillaries, venules, and lymphatics grows into this substance. The whole thing is maintained in a firm mass of gel. One might visualize the connective tissue as being a living mass of fibers and vessels all sitting in a mass of firm Jello. The ground substance is thus situated between the circulations and parenchymas and is subject to the action of both.[4]

Edema is the main pathology in allergy. Reinhart[9] has found, by metachromatic staining methods, that this pathologic allergic edema occurs where normally the mucopolysaccharides occur. Some of the examples that he gives are as follows: in eczema and urticaria, the edema is in the subepithelial reticular tissue; in asthma, the pathology is in the subepithelial mucopolysaccharides and in the gel between the smooth muscle fibers; in nasal allergy, the edema is in the amorphous substance of the subepithelial connective tissue. In short, allergic edema is found clinically where normally we have hyaluronic acid.

In all tissues there is a constant build-up and breakdown through certain enzyme reactions. This is true of ground substance. We do not know the enzyme mechanism in the build-up of mucopolysaccharides, but the breakdown is done through the action of the enzyme hyaluronidase (perhaps other minor enzymes also).[2] Hyaluronidase, sometimes called the spreading factor, liquefies the gel, making the connective tissue edematous. In order for this continuous enzymatic build-up and breakdown of the ground substance to take place, the enzymes must be present in or near the substrate tissue in bound form at all times. Thus they might be liberated or activated, instantaneously, in any inflammatory reaction of the tissues. Mayer's[7] work shows that in allergic and nonallergic inflammation of the skin, hyaluronidase is increased forty-fold. He also found that, unlike histamine, the spreading factor participates actively in the inflammation. In other words, in an allergic skin reaction, hyaluronidase is liberated in large amounts from the tissue of the inflamed area. It is not brought in by the blood stream, since practically none can be demonstrated in the circulation. Of course, other substances such as histamine, leucotaxine, et cetera, may also be liberated in the inflammatory reaction. When extra hyaluronidase is added to the sensitizing agent, the allergic skin inflammation is increased even more, and this increase is overcome by antihistamines.[7] Hence antihistamines are antihyaluronidases, and the latter may be the main factor in their control of allergic symptoms.

Zweifach and Chambers[13] have found that hyaluronidase has no effect on the intercellular cement of the capillary wall but does increase capillary permeability by liquefying the gel around the capillary. The nature of intercellular capillary cement is not known, but it apparently is not hyaluronic acid, and hyaluronidase does not act on it as such.[1]

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Now, what is known about factors that inhibit the spreading power of hyaluronidase? Normal serum contains antihyaluronidase.[3] Serum antihyaluronidase varies in certain disease conditions. For example, it is high in acute rheumatic fever but comes down on recovery. Successful ACTH and cortisone therapy also bring down the serum antihyaluronidase. This would indicate nature's protective mechanism in certain sensitivity states. The amount of serum inhibitor may reflect the state of the connective tissue. It is well known that the pathology in rheumatic fever is located mostly in the amorphous substance.

Opsahl, White and Duran-Reynals[8] have shown that, *in vivo*, ACTH and cortisone have marked antihyaluronidase activity. Their experiments show that if dye plus hyaluronidase is injected into the skin of an animal, there is a marked increase in the spread of the dye as compared to its injection alone. This increased spread by hyaluronidase is easily overcome if the animal is given cortisone. Also, if an animal is adrenalectomized and the dye is injected into the skin, there is a marked increase in the spread of the dye. This increase is overcome by giving cortisone to the animal. Thus, *in vivo*, cortisone and ACTH are marked antihyaluronidase factors, and this is probably their action in overcoming allergic edema.

A brief summary of this discussion so far follows:

1. Edema is the main pathology in allergy.
2. Allergic edema occurs where we normally have the hyaluronic acid gel of connective tissue.
3. The enzyme hyaluronidase which liquefies hyaluronic acid is present in large amounts in bound form in or near the gel of connective tissue.
4. Hyaluronidase is increased forty-fold in allergic skin inflammation.
5. ACTH and cortisone overcome the action of this hyaluronidase spreading factor.

Now, are there any other possibilities as to the mechanism of action of these hormones? The quite varied reports on antibody formation show that ACTH and cortisone do not function in allergy by any change in specific antibody formation. Since Landau et al[6] have shown that these hormones do not protect animals from anaphylactic shock, then ACTH and cortisone do not interfere with the antigen-antibody reaction. Landau[6] has also shown that these hormones do not interfere with the histamine wheal and that they do not protect from histamine shock. Hence they do not block or neutralize histamine. Code has shown that cortisone does not interfere with the release of histamine in the antigen-antibody reaction. Anyway, histamine is very likely only of secondary importance in the allergic reaction, being one of the many things liberated in tissue damage from any inflammation. Therefore, our only logical site of action of ACTH and cortisone is in the ground substance of the connective tissue.

I would like then to present the following hypothesis as to a fundamental

mechanism in allergy. In the tissue damage from an allergic reaction (antigen-antibody union, stress from any factor such as emotional strain, overwork, exposure to cold or dampness or other physical factors) hyaluronidase is liberated from the damaged tissue, and this liberated enzyme produces the allergic edema which is the main pathology in allergic inflammation. The hormonal system (ACTH and cortisone) makes up the physiological antihyaluronidase system to overcome this edema. However, certain allergic individuals inherit a dysfunction of the autonomic nervous system. The autonomic nervous system regulates and is part of the hormonal system. With this autonomic dysfunction there is a failure to produce, in allergic people, the proper amount of antihyaluronidase hormones to overcome the edema. It is possible that the allergic state is characterized by a local *imbalance* in the connective tissue enzymes in which hyaluronidase overpowers the building-up enzymes. Hence, an excessive amount of adrenal cortical hormone is required to maintain good gel and eliminate allergic edema in the shock organ.

SUMMARY AND CONCLUSION

1. Edema is the main pathology in the allergic state.
2. Clinically, allergic edema is located in the mucopolysaccharide gel of connective tissue.
3. The enzyme hyaluronidase liquefies the mucopolysaccharide gel of connective tissue and thus produces edema.
4. Hyaluronidase is present, in bound form, in or around connective tissue at all times.
5. This enzyme is liberated from damaged tissue in large amounts in allergic inflammation of the skin. Thus, in allergic inflammation hyaluronidase is available for the production of allergic edema.
6. *In vivo,* ACTH or cortisone neutralizes hyaluronidase and restricts allergic edema.
7. Normally there is an equilibrium in the enzyme action which builds up and breaks down hyaluronic acid. Thus, even while under stress, a firm normal connective tissue gel is maintained in nonallergic individuals.
8. However, in the allergic state (a) either the breaking-down enzyme, hyaluronidase, overbalances the building-up enzymes of connective tissue gel, thus requiring an excessive amount of cortisone to maintain equilibrium, or (b) possibly there is a dysfunction in the autonomic nervous system and hormonal system in which not enough cortisone is produced to maintain equilibrium.
9. This hypothesis suggests that the allergic state is characterized by a condition in which many types of stress produce an imbalance in the building up and breaking down enzyme systems of the amorphous substance of the local shock organ. The localization in certain shock organs is probably brought about through the action of the autonomic nervous system.

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ADDENDUM

I agree with Williams[12] that the evidence now available indicates that Von Pirquet's hypothesis is no longer adequate to meet all phases of clinical allergy.

Many allergic humans *do* form sensitizing antibodies to small amounts of so-called harmless substances. In many the antigen-antibody union *does* produce stress with tissue damage and edema. However, in others, the same tissue damage and edema will develop from other physical or emotional stress and without the antigen-antibody mechanism. The antigen-antibody mechanism is only one specific type of stress that produces pathology in allergic humans.

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EFFECT OF TOBACCO ON LUNG-VOLUME

The authors determined the total lung-volume, as well as the vital capacity, the complemental air, the reserve air, the functional residual air and the residual air, in a group of fifty-eight healthy male subjects, correlating the results with the patient's present and past consumption of tobacco. The findings show clearly that smoking produces a diminution in the vital capacity, and a more pronounced increase in the residual air, and in the ratio of residual air to total lung-volume. Smoking also produces a diminution in chest expansion.

A lessened vital capacity and an increased residual air have long been known to be associated closely with a reduction in ventilatory efficiency. The changes produced by smoking appear to be reversible, since ventilatory efficiency seems to improve when the patient stops smoking.—Whitfield, A. G. W.; Arnott, W. M.; and Waterhouse, J. A. H.: The effect of tobacco on lung-volume. Quart. J. Med., 20:141 (Apr.) 1951.

STUDIES OF CAPILLARY RESISTANCE IN ALLERGIC STATES

I. The Gothlin Index in Allergic Disease

HYMAN SHERMAN, M.D., F.A.C.A., THEODORE D. COHN, M.D., and JEROME SHERMAN, M.D.

Brooklyn, New York

IT was pointed out by Osler that there was a group of purpuric cases which appeared to have an allergic basis. In recent years there have been numerous reports indicating that the nature of vascular changes leading to transudation and hemorrhage is often allergic. In addition to hemorrhagic manifestations, other allergic phenomena such as urticaria, angioneurotic edema, and asthma may be present. In most cases of allergic purpura a food or a drug allergy has been the offending agent. In 1914 Osler predicted that "the anaphylactic key will unlock the mystery of these cases." Duke[1] observed abdominal cramps, urticaria, and purpura in a woman allergic to rice. Thomas and Forsythe[4] reported ten patients with purpura hemorrhagica, all of whom had other evidences of allergy. Eight of these patients had a positive family history of allergy. The concept that certain types of purpura, urticarial wheals, angioneurotic edema, and erythema nodosum might all be based on the same mechanism of increased capillary fragility or permeability due to allergic states has been fairly well accepted. Griffith[2] has shown that capillary fragility or permeability may be due to involvement of the intracellular cementum because of a lack of vitamin P. This state may be overcome at times by using rutin, a vitamin P-like substance related to the flavones. He used the Gothlin[3] index as a quantitative measure for capillary resistance. Low capillary resistance has been recorded in many diseases, some of which are scarlet fever, measles, scurvy, rheumatic fever, bronchopneumonia, thrombocytopenic purpura, hypertension, diabetes, peptic ulcer, the colitides, and arteriosclerosis, as well as during menses and the premenstrual phase, and in senility and vascular allergy.

Because of the association of allergic purpura with other manifestations of hypersensitivity, and because of the diverse syndromes producing lowered capillary resistance, and further because of Griffith's observations, it was decided to make a routine study of capillary fragility in patients appearing at an allergy clinic. The Gothlin index was used as a quantitative yardstick because of Griffith's work and because of its popularity as a measure of capillary resistance.

PATIENTS STUDIED AND TECHNIQUE

Forty-eight consecutive allergic patients appearing at the Allergy Clinic were studied (Table I). There were twenty males and twenty-eight

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From the Allergy Clinic and Department of Medicine, Coney Island Hospital, Brooklyn, N. Y.

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females. Ages ranged from six to seventy-three years with an average age of twenty-nine. There were nineteen patients with hay fever, seven with asthma, seven with hay fever and asthma, eight with allergic rhinitis, seven with urticaria and angioneurotic edema, and one with contact dermatitis. Each case was surveyed medically to rule out any other organic disease which might interfere with the study. Except for the degenerative process of arteriosclerosis in the older age group no organic disease was found.

TABLE I. CASES STUDIED

Type of Case	No. of Cases
Hay Fever	19
Asthma	6
Hay Fever and Asthma	7
Allergic Rhinitis	8
Urticaria and Angioneurotic Edema	7
Contact Dermatitis	1
Total	48

TABLE II. RESULTS OF FINDINGS

Index Found	No. of Cases
0	14
1	4
2	8
3	9
4	4
5	5
6	2
7	1
9	1
2.3	Average

The Gothlin index was performed on each patient according to the following technique,[5] and an average of two readings per patient was performed, one on each arm; and in several this procedure was repeated on two separate occasions.

A circle 6 cm in diameter was marked off on the forearm anteriorly at the elbow. Any marks within this area which might later be confused with petechiae were noted. Using a blood pressure cuff above the elbow, a pressure of 35 mm of mercury was maintained for fifteen minutes. The pressure was then lowered, and the petechiae were counted in good light with the aid of a magnifying lens. The blood pressure cuff was then reapplied and the pressure maintained at 50 mm pressure for fifteen minutes. The pressure was lowered again, and the petechiae were again counted. The Gothlin petechial index was then calculated. This index was determined by multiplying by two the number of petechiae found at 35 mm pressure and adding the number of petechiae found at 50 mm pressure. The normal index is 8 or less. An index of 9 to 12 was considered borderline. An index of 13 or over was considered abnormal.

RESULTS

In this series of forty-eight cases there were no cases in which the Gothlin index was found to be abnormal (Table II). The highest index

was found to be 9 in a woman of twenty-five with hay fever. In fourteen cases the index was 0. The average index for this group was 2.3. There was no correlation between the type of allergy and the petechial index. In one instance of drug allergy (asthma) in a girl of ten, a provocative test of 2½ grains of aspirin produced mild asthma and headache. The Gothlin index was found to be 0 during the reaction of the drug.

In order to test the validity of this technique as an index of capillary fragility, five control cases were studied. The first case was a man, seventy-six years of age, with arteriosclerosis who showed a mean average in both arms of fifteen petechiae. One case of iodiopathic thrombocytopenic purpura (Werlhoff's disease) showed a tremendous number of petechiae, too many to count but well above any normal range; one case of hypertension showed no petechiae; one case of diabetes showed none, and one woman, aged thirty, who had spontaneous ecchymosis during menstruation showed a petechial index of 13. Thus we believe that the Gothlin index was a fairly valid test.

DISCUSSION

There are conflicting reports in the literature as to the question of capillarly resistance in allergic states. There is no standard technique for capillary resistance studies. Thus final conclusions cannot be drawn until a basic acceptable and reliable method is established and standardized. The Mt. Sinai group found a high incidence of lowered capillary resistance in their series of cases, but they did not use the Gothlin index. There are several techniques for testing capillary resistance; and when there are numerous procedures for the study of any biological phenomenon, no method is completely valuable. Thus far, the methods have been too general and subject to too many variables. Most techniques, however, embody the principle of capillary strength and depend upon the production of skin hemorrhages, presumably due to a rupture of the capillary wall. Some of the methods are as follows: (1) a suction method called the capillary resistometer or petechiometer; (2) the Rumpel-Leede test, of which the Gothlin index is a more accurate modification; (3) direct capillary observation of the affected vessels in the nail beds; (4) the puncture test, in which the skin is lightly pricked with a fine needle, and if on the following day fine bleeding points are visible at the sites of puncture points, then the patient has a tendency to bleed; and the test of Peck, Rosenthal and Erf, which is a skin test based on the principle that the venoms of various species of snakes produce hemorrhagic toxins.

In view of these varied techniques we feel that before a final statement can be made as to the true picture of capillary resistance in the allergic state, a complete survey using all methods of study must be made. This work is presently in progress.

In this series of cases, seven cases of urticaria and angioneurotic edema were studied. Theoretically, if the concept of increased capillary permeabil-

ity or fragility is correct for hemorrhagic allergic states and urticaria and angioneurotic edema, then there should have been a fairly high number of positive Gothlin indices in these cases. All, however, were negative. This brings up the point as to whether capillary fragility and permeability are the same thing.

It is the concept of the authors that there are two separate phenomena in the pathological physiology of the capillaries. Capillary permeability is an index of transudation through the capillary well, producing wheals and edema of the skin. Capillary fragility is a measure of capillary strength; and when weakened by a possibly allergic mechanism, the capillary ruptures, producing minute hemorrhages. It has been said that fragility and permeability are a quantitative matter of degree of the severity of the disease process in the capillary. Thus in angioneurotic edema and urticaria simple serum transudes through the capillary wall, and in more severe states there is a diapedesis of red cells through the capillary wall or the intercellular cementum. Griffith's work negates this concept. Direct visualization of the petechiae under the microscope as introduced by Cutter and Marquand shows the rupture point in the capillary.

SUMMARY

1. Forty-eight consecutive allergic patients appearing at an allergy clinic were studied for capillary fragility, using the Gothlin technique as the index of resistance. In this series there were no cases that demonstrated decreased capillary resistance.

2. The other methods employed for the study of capillary weakness have been mentioned.

3. The possible reasons for conflicting reports in the literature have been discussed.

CONCLUSION

In routine allergic states, using the Gothlin index as a measure, we have been unable to demonstrate capillary weakness. We are unable to say what other techniques may show, and this is a subject for future investigation.

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455 Ocean Avenue

A COMPARATIVE STUDY OF EFFECTS OF CERTAIN ANTIHISTAMINES ON SKIN REACTIVITY

I. A. FOND, M.D., F.A.C.A.
Chicago, Illinois

THIS study constitutes an attempt to find a suitable antihistamine which will depress the skin reactivity of the atopic patient to such a degree that it will be of marked value in pronounced dermographism. Evaluation of the drug to include the degree and length of depression produced with minimum side reactions. Four drugs have been investigated in this study: namely,

1. Perazil® (Di-paralene)
2. Chlor-Trimeton®
3. Pyribenzamine®
4. Benadryl®

METHOD

Five serial dilutions of ragweed extract, Endo dust, and histamine in multiples of five were injected intradermally. The strongest ragweed extract dilution of the series used was 1:10,000, that of Endo dust 1:1,000, and that of histamine base 1:10,000. Twenty-five patients known to give positive skin reactions to ragweed extract and twenty-five known to give positive skin reactions to house dust were tested. Simultaneous intradermal injections of 0.02 cc. of each of the serial dilutions of histamine were made on one side of the forearm and of ragweed extract or Endo dust on the other side of the forearm. Tracings of the wheals and erythemas were transferred to paper ten minutes after the intradermal injections. Each of the patients received one of the antihistamines orally in the following doses:

1.	Perazil	50 mg or 100 mg
2.	Chlor-Trimeton	4 mg
3.	Pyribenzamine	50 mg
4.	Benadryl	50 mg

At the end of an hour intradermal injections of the same serial dilutions were made on corresponding sides of the other forearm. Ten minutes later

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From the Outpatient Treatment Department, Veterans Administration Regional Office, Chicago, and the Department of Medicine, Northwestern University Medical School of Chicago.

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tracings were again made and the results recorded as before and compared. The results were classified on the basis of a minimal skin test dose, which was defined as the first concentration of the antigen used which produced erythema and whealing. When the next stronger concentration was required to produce an erythema of corresponding size, it was designated as

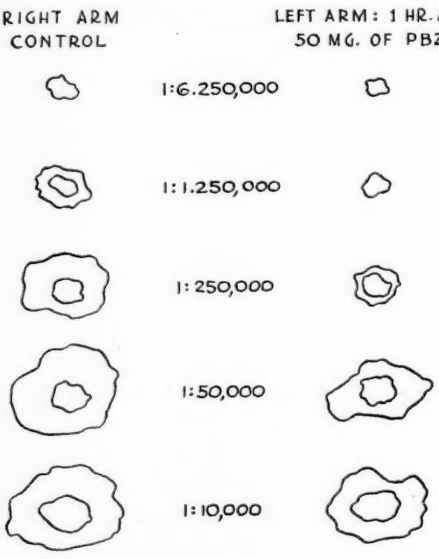

Fig. 1. Tracings of whealing and erythema produced by intradermal injections of serial dilutions of ragweed extract.

a moderate decrease, and when a still stronger concentration was needed, it was recorded as a marked decrease. Tracings were also made at longer intervals, e.g., from two to twelve hours, of intradermal injections after Perazil and Chlor-Trimeton.

RESULTS

Figure 1 shows a representative titration with ragweed extract and Pyribenzamine:

Table I shows the comparative results of tests with the dilution of ragweed extract after the administration of the four anti-histamines used in this study.

Table II shows the results obtained when serial dlutions of Endo dust were used.

Table III shows the results using dilutions of histamine.

Table IV shows the relative decrease in skin reactivity to serial dilutions

TABLE I. EFFECT OF ANTIHISTAMINES ON SKIN REACTIVITY TO RAGWEED EXTRACTS AFTER ONE HOUR

	Total Tests	No Decr.		Mod. Decr.		Mkd. Decr.	
		T	%	T	%	T	%
Perazil	59	29	49	20	34	10	17
Chlor-Trimeton	35	13	37	12	34.3	10	28.7
Pyribenzamine	30	12	40	9	30	9	30
Benadryl	26	8	30.7	8	30.7	10	38.6

TABLE II. EFFECTS OF ANTIHISTAMINES ON SKIN REACTIVITY TO ENDO DUST AFTER ONE HOUR

	Total Tests	No Decr.		Min. Decr.		Mkd. Decr.	
		T	%	T	%	T	%
Perazil	65	43	66	15	23	7	11
Chlor-Trimeton	44	20	45.5	15	34.1	9	20.4
Pyribenzamine	43	20	46.5	15	35	8	18.5
Benadryl	33	10	30.3	16	48.2	7	21.5

of ragweed extract and Endo dust at four, eight and twelve-hour intervals after oral administration of Perazil.

As seen from these tables, Pyribenzamine, Benadryl and Chlor-Trimeton showed the greater effect on the skin reactivity, one hour after oral administration of the antihistamine. Perazil in 100 mg doses showed its greatest effect four to eight hours later. However, Pyribenzamine had the most effect in depressing the reactivity of histamine. Perazil was found to exert a depressant action greater than that of Chlor-Trimeton when the tests were repeated after a two-hour interval or longer. Of course, one must remember that the dose of Perazil administered on retiring was twice the dose of the other antihistamines used.

The most objectionable effect from the administration of these antihistamines was the complaint of drowsiness. This was most evident after Benadryl and Pyribenzamine and was less evident when Perazil was given on the night prior to the performance of the tests. Only one patient complained of feeling jittery after the administration of Pyribenzamine.

DISCUSSION

The antihistaminic drugs have been classified by Seyler[8] into four groups, according to their chemical formula: e.g.,

1. Benadryl Group
2. Pyribenzamine Group
3. Histadyl Group
4. Miscellaneous Group, such as Trimeton, Perazil, et cetera.

According to Serafini,[7] orally administered antihistamines will constantly inhibit histamine and allergic flares and wheals, as was shown by comparing

TABLE III. EFFECTS OF ANTIHISTAMINES ON SKIN REACTIVITY TO HISTAMINES AFTER ONE HOUR

	Total Tests	No Decr. T	No Decr. %	Mod. Decr. T	Mod. Decr. %	Mkd. Decr. T	Mkd. Decr. %
Perazil	43	34	79.5	8	18.5	1	2
Chlor-Trimeton	36	19	52.5	7	20	10	27.5
Pyribenzamine	35	12	34.3	15	43	8	22.7
Benadryl	29	10	34.5	9	31	10	34.5

TABLE IV. RELATIVE DECREASE IN SKIN REACTIVITY TO RAGWEED EXTRACT AND ENDO DUST AFTER 100 MG PERAZIL ORALLY

Total	4 Hr.		8 Hr.		12 Hr.	
	T	%	T	%	T	%
88	25	28	35	40	28	32

the tracings of histamine and allergic wheals obtained by intradermal tests technique before and after the antihistaminic drugs were administered. The maximum effect occurred two to four hours after oral administration of the drugs. Our experiments showed a variability in the time period when the maximum effect was apparent.

Baer and Sulzberger[3] indicated that Pyribenzamine produced a marked reduction in the urticarial response fifty minutes after 150 mg of the drug was given, with no apparent effect upon the degree, course, or duration of the fully formed dermographic wheals elicited by a stimulus applied before the administration of the antihistamines. Arbesman et al[2] demonstrated a definite decrease in the size of the wheal, forty-five minutes after oral Pyribenzamine in doses of 50 to 150 mg, produced by intradermal injections of serial dilutions of histamine. The results of our experiments indicate a corroboration when testing was done sixty minutes after oral Pyribenzamine.

Lovejoy, Feinberg and Canterbury[6] have shown that the antihistaminic drugs inhibit the local allergic reactions. They state that the degree of the histamine reaction is not necessarily synonymous with it. This has been corroborated in this study.

Allison and Robinson[1] showed that Chlor-Trimeton inhibited histamine and antigenic whealings. Our results indicated that the greatest effect of the drug could be demonstrated two to three hours after the oral administration of the antihistamine.

Feinberg and Friedlaender[5] were able to prevent the demographic response in patients undergoing allergy skin tests by giving 50 to 150 mg Benadryl a few hours prior to skin testing. The drug did not interfere with the production of the specific skin reactions to the antigen. However, untoward side effects were produced, such as sleepiness and lassitude.

Feinberg[4] found that the ability of Perazil to inhibit the wheal response to histamine showed marked variabilities not encountered in similar studies with other antihistaminic drugs. In some subjects the maximum effect was obtained in one hour, in others in two to three hours. The duration of effects in some cases was four hours, while in others it was eight to eighteen hours. Our findings led us to the same conclusions.

CONCLUSIONS

1. Perazil caused no reduction in skin reactivity one hour after administration of the drug but was most effective after six to twelve hours.
2. Chlor-Trimeton was most effective from one to two hours, and its effects, at times, lasted as long as four hours.
3. Pyribenzamine and Benadryl showed the greatest effect one hour after oral administration, and their action waned within two to three hours.
4. All of the antihistamines produced some unpleasant side reactions, such as dizziness and headache and especially drowsiness which was most objectionable.
5. The drug of choice to be used in dermographism, as determined by this experiment, apparently was Perazil in a dose of 100 mg administered on the preceding night. At the time of the skin testing the unpleasant side reactions were not evident, but the skin reactivity was nevertheless sufficiently depressed to give more accurate readings.

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MEDICAL ASPECTS OF CIVIL DEFENSE

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THE USE OF HISTAMINE IN THE TREATMENT OF ALLERGIC DISEASES

HINTON D. JONEZ, M.D., F.A.C.A.
Tacoma, Washington

HISTAMINE (beta-iminazolylethylamine) was first prepared synthetically by Windaus and Vogt[91] in 1907. Barger and Dale[11] isolated it from ergot in 1910. In 1927 Best, Dale Dudley and Thorpe[14] demonstrated its presence in living tissue. Very little therapeutic value was attributed to histamine until the work of Horton began in 1927. Since that time the acceptance of histamine as a drug of therapeutic importance has been slow. This is probably due to the fact that as a therapeutic agent, its action is not definitely selective. It was thought that histamine was present in all human tissue until Kwiatkowski[55] in 1943 showed that it was not present in the central nervous system or peripheral motor nerves. In health the amount in human blood ranges from 1 to 8 micrograms per 100 cc of blood.[16,73]

The principal reason that the action of histamine in man is misunderstood is that its action on laboratory animals is at times exactly the opposite of what it is in man. Goodman and Gilman[37] point out that the action of histamine on the arterioles changes as one ascends the zoological tree. For example, in rodents the drug produces marked arteriolar constriction; in cats, a slight arteriolar constriction; in the dog, monkey and man, arteriolar dilatation. In man there is very little fluctuation of the histamine contents of blood in normal persons.[70] In allergic diseases there is markd fluctuation.[53,65] In asthma, eczema or vasomotor rhinitis, there is an increase of histamine in the blood content. This increase is more marked in young allergic patients than in older ones. An exception to this increase of the blood histamine level is found in angioneurotic edema and serum sickness during attacks. The blood histamine level usually returns to normal when the symptoms subside.

Little is definitely known as to where the histamine in the body comes from. One theory is that it is all absorbed from the intestinal tract like a vitamin.[34] It is then stored in the tissues in combination with some substance that inactivates it. This substance has as yet never been isolated. We know that the body of a cat, for example, contains enough histamine to kill the cat, but we do not know why it does not normally do so. In the circulating blood there is a comparatively low concentration normally present in the plasma. When human blood is centrifuged most of the histamine is found in leukocytes. It is probably in the granulocyte cells. It seemed probable at one time that most of the histamine was in the eosinophil cells.

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Dr. Jonez is Medical Director of the Multiple Sclerosis Clinic, St. Joseph Hospital, Tacoma, Washington.

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The theory has now been discredited since Rose[76] (1950) caused a complete disappearance of eosinophils from the circulating blood by injecting the adrenocorticotropic hormone (ACTH) without any clear effect on the blood histamine.[34]

The pharmacological and clinical actions of histamine are many, the principal one being a powerful dilatation of the capillaries[25,27,80,84,86,87,89,90] so that their permeability is increased. This results in a fall in blood pressure which may be very marked. There is usually also a flushing of the skin. Smooth muscle is also stimulated directly, causing the muscles of the stomach wall and of the bronchioles to contract markedly. Histamine acts as a powerful stimulator of secreting glands, especially those of gastric secretion. However, as allergists we are more interested in a different clinical phenomenon of this many-sided drug.

Horton has long looked upon histamine as the common denominator of allergic disease, and of some diseases not now recognized as being allergic in nature.[43] The advent of the antihistaminic drugs has increased markedly the interest and knowledge of both the laity and the medical profession concerning allergic conditions. These drugs have also pointed out to the profession the role of histamine in allergy.

Injections of histamine when first administered to a patient, if in sufficient amount, will usually produce the symptoms of allergy from which the patient has suffered. Therefore, the reasoning that when the allergic insult occurs, whether it be pollens, epidermals, molds, drugs, or some other, some of the cells of the allergic individual release histamine with a resulting antigen-antibody reaction[46] in the same manner as when anaphylactic shock occurs. There is much evidence to suggest that the mechanism involved in anaphylaxis and allergy[19,20,23,31,33,54,68,69,72,76] is a manifestation of the same phenomenon. The normal individual is usually able to produce just sufficient antibody reaction to neutralize the effect of the antigen. The allergic individual produces an excess of antibodies, and this surplus of antibodies attach themselves to cells of the "shock tissue," rendering them sensitive or allergic to further stimulation by the "aggravating antigen."[26]

Cutner[24] explains hypothetically the role played by histamine in the production of allergic symptoms as follows:

(a) All tissue cells, allergic or not, contain intracellular histamine or histamine-like substance. This has no effect while within the cells.

(b) When sensitized as above, allergic cells have "antibodies" attached to them.

(c) When the "aggravating antigen" reacts with the antibodies attached to the sensitized cells, the histamine or histamine-like substance contained in the cells is liberated.

(d) The liberated histamine acts on the cells, depending on the individual, producing its characteristic reactions, thus causing the particular symptom of the "allergy," e.g., urticaria, asthma, et cetera.

Support for this hypothesis, as stated above, is found in some of the methods used to prevent the appearance of the symptoms. These consist essentially in the prevention of histamine liberation and/or the control of its actions.

Of recent years the most prevalent method of control is by the administration of the various antihistaminic drugs.[18,32,59,61,62,77] Of course, the relief is merely temporary. Therefore, they must be taken regularly for prophylaxis or treatment of attacks. Formerly, neutralizing drugs were largely used, such as atropine and epinephrine. Then, attempts have been made to hyposensitize with increasing minute quantities of liquid extracts of the aggravating antigens. This method produces very good results most of the time if the definite aggravating antigen can be found.

When the latter method is unsuccessful or the substance causing the aggravating antigen cannot be discovered, hyposensitization by histamine is frequently and dramatically successful. There are many theories regarding histamine hyposensitization. The older one is well stated by Cutner[24] to the effect that since the liberation of histamine in the body is considered to be a common factor in all the manifestations of allergy, it is reasonable to assume that if, instead of trying to isolate the particular antigens, we train the organism to protect itself against the liberation of histamine, then we should cure, or at any rate relieve, the patient's condition. The usual method of training the body is to give increasing doses of histamine. This has been done for some time and has given good results in many cases. The action is assumed to be due to the production of an antibody which, by attaching itself to the already sensitized cells, prevents the union of the "aggravating antigen" with the antibody producing the sensitivity and thus prevents the liberation of the histamine from the sensitized cell. The great advantage of the use of histamine hyposensitization over the use of antihistamines suggested by the foregoing hypothesis is that it implies the possibility of a cure. Rose[72] points out that while tissue damage of a permanent nature, with associated morphologic changes, may arise from antigen-antibody reaction, these changes do not result from the administration of histamine itself. More recently Horton postulated[43] regarding the action of histamine on the glands of internal secretion in man as follows: histamine causes the liberation of epinephrine from the medullary portion of the suprarenal gland activating the suprarenal cortex. He further says it would seem as if the cortical discharge of steroids in man occurs more promptly following the administration of histamine than it does after the administration of any other agent thus far tested. Many of the phenomena observed after the clinical use of compound E (cortisone) and ACTH have been observed after the clinical use of histamine.

We ourselves have had many similar experiences. One is as follows: in 1947 a woman was brought to us in a nearly moribund condition, suffering from coccidioidomycosis. She was bronze to copper hue. Her eosinophil count was very high. Her metabolic rate was also very high. Hers was

the disseminating type of coccidioidomycosis usually considered lethal. Due to the high eosinophil count and the positive skin test for coccidioidomycosis, we felt that the giving of histamine intravenously might be tried. She was given histamine intravenously daily in the usual manner, with the bronzing disappearing in a few days; and at the end of about two weeks her condition was so markedly improved that we called several consultants together in an effort to analyze how and why histamine was acting as it did. This improvement continued, and the case was reported by title at the annual meeting of The American College of Allergists in 1948.[48] The patient continued on histamine for several months, at first daily and then three times a week, returning to apparently normal health and strength. When she became tired of the continued histamine routine, we unfortunately permitted her to take a week's vacation. On the fifth night of this vacation, her relatives frantically telephoned, stating she had gone into a state of collapse. She was ordered back into the hospital immediately, and intravenous histamine was started at once. However, she expired quickly, dying a typical Addisonian death. On autopsy it was found that both suprarenals were involved in coccidioidal granulomas. Undoubtedly there was just sufficient medulla and cortex left so that by the stimulation of histamine sufficient cortisone was produced to continue life, in the same way that cortisone given now in Addison's disease keeps the patient alive.

We were at a loss to explain the mechanism by which histamine produced the results similar to those seen now following the use of cortisone or ACTH.

Recently, Stefanic and Loyke[82,83] advanced the idea that histamine, when injected either by direct stimulation or through vasodilatation on the suprarenal medulla, causes an added release of epinephrine, which then stimulates the anterior pituitary through the hypothalmus to produce ACTH, that in turn activates the suprarenal cortex in the release of cortisone and other factors.

It is our opinion that histamine when properly given not only acts on allergic conditions by activating the suprarenals as described above, bringing about rapid temporary relief many times, but also hyposensitizes in the manner of the earlier conception of its action. These beneficial results in the diseases of allergy are accomplished without any deleterious side actions of either a temporary or a permanent nature.

Over 2,000 patients with many different allergic conditions have been treated personally by us, using all of the known methods of histamine administration. Never once have we seen any undesirable temporary reaction that could not be controlled by epinephrine; further, we have never seen any permanent undesirable result.

Histamine is given usually by one of four different methods: namely, subcutaneous, intravenous,[8,13,41,42,44,45,47,64,74] deep intramuscularly, and by iontophoresis.[3,4,5,6,49] It is relatively ineffective by mouth, owing to its rapid

TABLE I. 2.75 MG HISTAMINE DIPHOSPHATE IN 250 CC NORMAL SALINE, INTRAVENOUSLY 45 DROPS PER MINUTE FOR 1½ HOURS

Name	Before Volume Per Cent	During Volume Per Cent	Finish Volume Per Cent	1 hour later Volume Per Cent
R.W.	10.8	15.3	16.8	11.2
M.A.	10.3	15.7	16.3	10.1
W.M.	9.4	16.1	13.6	9.9
E.M.	9.4	15.5	9.9	8.2
H.C.	13.5	18.3	17.6	13.7

TABLE II. 11.0 MG HISTAMINE DIPHOSPHATE IN 1000 CC NORMAL SALINE, INTRAVENOUSLY 45 DROPS PER MINUTE FOR 6 HOURS

Name	Before Volume Per Cent	2 hours Volume Per Cent	4 hours Volume Per Cent	6 hours Finish Volume Per Cent	2 hours later Volume Per Cent
J.T.	10.6	16.9	18.2	19.1	8.4
J.W.	12.6	17.5	17.8	18.0	8.1

TABLE III. .275 MG PER CC HISTAMINE DIPHOSPHATE SUBCUTANEOUS INJECTION

Name	Before Volume Per Cent	1 hour after Volume Per Cent	2 hours Volume Per Cent	3 hours Volume Per Cent	4 hours Volume Per Cent
W.M.	10.2	11.6	11.5	11.0	10.2
M.A.	10.5	11.8	11.5	9.0	9.9
R.W.	10.4	11.5	12.6	11.0	10.6

destruction in the intestines. Histamine diphosphate is the salt which is used; 2.75 mg of this salt equals 1 gram of base histamine.

It is impossible to gauge the therapeutic effects of histamine by direct laboratory methods,[28,29,57,60,66,67,71] because it is very rapidly destroyed in the blood stream by the enzyme histaminase.[1,7,12,15,21,22,50] We must therefore depend upon gauging the length of the drug's effectiveness by measuring the length of time vasodilatation continues after its administration. This can be measured by the increased oxygen content of the venous blood. In 1944 Peters, Horton and Boothby[63] had shown an increase in oxygen consumption during intravenous histamine injection (Van Slyke gasometric method.) Also, in 1947 Grob, Lilienthal and Harvey[36] reported measuring the histamine-like effects of an aqueous solution of curare by blood oxygen content (method not stated). We made a study of all of the various methods of histamine administration, gauging them by the increase in the oxygen content of the venous blood. The Van Slyke volumetric apparatus was used. The oxygen content of venous blood varies normally from 10 to 18 volumes per cent, arterial blood normally 15 to 23 volumes per cent. The results of our studies are shown by Tables I to VI.

Subcutaneous injection vasodilatation lasted on an average of about three hours following the injection. The intravenous method, while causing a markedly greater vasodilatation, continued the dilating effects for only about one hour. By iontophoresis the vasodilatation equaled the intravenous vasodilatation and continued above normal for over three hours. However, apparently the most effective method of all was the deep intramuscular injection of histamine diphosphate in a repository menstruum.

TABLE IV. BY IONTOPHORESIS 10 CC OF A 1% SOLUTION OF HISTAMINE DIPHOSPHATE AT 6 MILLIAMPERES FOR 15 MINUTES

Name	Before Volume Per Cent	During Volume Per Cent	After 15 Minutes Volume Per Cent	After 1 hour Volume Per Cent	After 3 hours Volume Per Cent	After 4 hours Volume Per Cent
G.G.	9.6	19.8	13.2	9.4	9.2	9.6
O.R.	11.7	18.2	18.7	15.5	12.2	11.4
M.A.	10.6	17.8	15.5	14.2	11.0	10.2
J.S.	10.8	20.8	19.3	15.6	10.4	8.4
E.M.	8.9	15.2	14.7	11.2	9.2	8.6
C.F.	10.2	13.9	13.9	13.4	10.5	8.4

TABLE V. ½ CC OF HISTAMINE DIPHOSPHATE IN A GELATIN-UREA SUSPENSION 3 MG PER CC

Name	Amount given of 3 mg Histamine Diphosphate in 5 cc Gelatin-urea	Oxygen per cent venous blood before	One hour later	2 hours	3 hours	4 hours
M.A.	.5 cc	14.6	20.3	13.7	10.4	13.7
H.J.	.5 cc	12.1	17.2	11.1	7.5	10.3
M.G.	.5 cc	9.1	16.7	12.3	8.9	9.1
E.I.	.5 cc	14.4	18.5	15.6	12.7	13.9
D.H.	.5 cc	9.9	16.3	13.2	9.4	9.9

TABLE VI. ½ CC OF A HISTAMINE DIPHOSPHATE OIL AND OXYCHOLESTEROL DERIVATIVES SUSPENSION 2.75 MG PER CC INJECTED DEEP INTRAMUSCULARLY

Name	Before Volume Per Cent	After 6 hours Volume Per Cent	After 18 hours Volume Per Cent	After 24 hours Volume Per Cent	After 48 hours Volume Per Cent	After 72 hours Volume Per Cent	After 96 hours Volume Per Cent
E.S.	11.4	16.2	16.2	16.4	16.4	12.9	11.6
A.K.	10.2	14.8	13.6	12.7	12.4	11.2	10.6
M.A.	10.6	16.0	18.3	18.7	15.6	15.0	11.2
W.M.	11.0	17.6	17.6	17.6	16.4	14.7	12.1

Two types of menstruum were used, one consisting of urea-gelatin[2] and the other being peanut oil and oxycholesterol derivatives.[50,52] Histamine in the urea-gelatin vehicle raises the venous blood oxygen content higher than by any other method and maintains vasodilatation for about two hours. While histamine in the oil menstruum does not produce as rapid a vasodilating reaction, after six hours the vasodilatation is equal to that of any other method of administration and maintains this vasodilatation up to ninety-six hours, indicating a very slow release of histamine in the body.[35,38,39,51,88]

The method of treatment varies according to the allergic condition being treated. Where rapid hyposensitization is indicated, as in migraine, Méniére's syndrome, angioneurotic edema, drug reactions, and in multiple sclerosis and other demyelinating diseases,[63,81] the intravenous method is the one of choice. This consists of giving 2.75 mg of histamine diphosphate in 250 cc of an isotonic sodium chloride solution as an infusion. The rate of flow should be adjusted so that 250 cc is administered intravenously by the gravity method in not less than ninety minutes. Another precaution should be taken when intravenous histamine is administered, in that there should be food in the patient's stomach at the time histamine is administered, so that the excess of gastric acid may be absorbed. If gastric distress occurs, an alkaline gastric sedative should be given.

Where slow, cautious hyposensitization is desired, the subcutaneous method is usually used, this method being very effective in dust allergies, pollenosis, sinusitis and migraine. The subcutaneous method is used extensively following a course of intravenous histamine therapy. The strength of solution used is 0.275 mg per cc. Besides the use of subcutaneous histamine as a follow-up of intravenous therapy, it is used very satisfactorily where slow hyposensitization is desirable, as in hay fever, sinusitis, dust and mold allergies, and dermatoses; with many it is a method of choice in migraine. The initial dose recommended is 0.05 cc; this is increased 0.05 cc daily for ten days or until 0.50 cc are being given. We never go any higher than this, although 1 cc is recommended by some clinicians. In our opinion two doses a day should be given, if tolerated, for about ten days. We never give more than 0.50 cc at any one dose and never more than 1 cc of this solution in one day. After improvement has been secured, a maintenance dose of 0.50 cc should be given one to three times weekly to maintain the histamine hyposensitizing action.

The iontophoresis method of histamine administration is one of driving a 1 per cent histamine diphosphate solution into the pores of the skin over a small area by electrophoresis, using a galvanic current. A histamine wheal is formed from which the histamine is absorbed slowly. We have used this method in the treatment of all forms of allergy satisfactorily, even in asthma,[93] where great care must be used in histamine administration. The iontophoresis method is used very successfully in maintaining hyposensitization following histamine intravenous administration. For the past fifteen or twenty years physical therapists have been giving histamine by iontophoresis for rheumatoid arthritis, producing the histamine wheal over the affected joint. In some cases their results were spectacular. The improvement in the rheumatoid arthritis was considered a result of the counterirritation brought about by the histamine wheal. However, in light of present knowledge we realize that the improvement is the result of histamine activating the suprarenals and pituitary so that cortisone is produced, giving relief in the same manner that an injection of cortisone does.[9,10,29,40,56,58,75,79,85,92]

The most desirable method of all, in our opinion, is the deep intramuscular one using the menstruum of peanut oil and oxycholesterol derivatives containing 2.75 mg histamine phosphate per cc. This preparation can be used in all forms of allergy due to its slow release over a long period of time. This preparation is marketed under the name of "Histapon."* It is a method of choice in asthma, hay fever, urticaria, various skin lesions due to allergy, and as a follow-up on the rapid hyposensitization by histamine intravenously. The patient is taught the technique of administrating the injections himself as a diabetic is taught how to use insulin. This makes frequent trips to the doctor's office unnecessary. As in the subcutaneous

*Manufactured by Endo Products, Inc., Richmond Hill, New York.

administration, the dose is increased slowly, beginning with 0.05 cc and increasing usually 0.05 cc daily; where it is not tolerated well, the increase should be slower. We never give over 0.50 cc, and when this amount is given, customarily it is every second day. Judgment must be used in arriving at the optimum dose of repository histamine, as individuals vary markedly in their therapeutic reaction to the drug in this form. The only way the amount of this optimum dose can be arrived at, is by careful study of the patient's symptoms and reactions.

No matter by what method histamine is given, headaches may occur. In case this reaction takes place, regardless of the method by which histamine is being given, the next dose following the headache should be only half as much; then an increase can be started from that amount. Should an alarming reaction, such as a severe headache, nausea, dyspnea, or an alarming drop in blood pressure, occur, epinephrine 0.25 to 0.50 cc of 1:1,000 solution should be administered subcutaneously. If the reaction occurs during the intravenous administration of histamine, the rate of flow should be reduced or stopped and then resumed a little later at a reduced rate.

Occasionally a patient's treatment schedule will have to be readjusted, due to his developing a sensitivity to histamine. When this happens, formerly we used whole suprarenal extract for hyposensitization; now we use cortisone, and this reduces the patient's histamine sensitivity, usually in three or four days. We give 100 mg of cortisone daily during this period, then resume our histamine schedule, starting at our low dose again and increasing at one half the usual rate.

CONCLUSIONS

During the past seven years we have administered histamine by the various methods, giving over 75,000 doses intravenously and at least an equal number by the repository method. With this experience we deem it an absolutely safe drug if ordinary care and intelligence are used. We have and have had over 1,500 patients on self-administration of this drug by either repository or iontophoresis methods. They have carried on in a very satisfactory manner. With this experience we believe that in the field of allergy histamine is proving itself to be the closest approach to an over-all hyposensitizer. It is not a cure-all, but in any allergic condition where the causative factor cannot be definitely demonstrated, histamine is certainly worth a trial.

It is our opinion that histamine when properly given not only acts on allergic conditions by activating the suprarenals, as described above, to bring about rapid temporary relief but also hyposensitizes. We hold this on the basis of what seems overwhelming clinical evidence in spite of the lack so far of a wholly tenable theory of the immunological mechanism involved.

The beneficial results in the diseases of allergy, both by hyposensitization

and suprarenal stimulation, are accomplished without any deleterious side reactions.

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1401 Washington Bldg.

A TECHNIQUE FOR MINIMIZING SEVERE AND CONSTITUTIONAL REACTIONS WHEN ADMINISTERING ALLERGENIC EXTRACTS SUBCUTANEOUSLY

NATHAN E. SILBERT, M.D., F.A.C.A.

Lynn, Massachusetts

IN 1949 a certain group of patients with seasonal allergic rhinitis, while undergoing seasonal treatment for their specific allergic disorders, received with the allergens an injectable solution of Chlor-Trimeton Maleate, an antihistamine with which we have had considerable experience.[9] This mixture was injected subcutaneously in the routine fashion. For purposes of comparison, another group was observed who were being treated in the usual manner with the offending allergenic extracts, without the injectable solution of Chlor-Trimeton Maleate. In 1950, because of the favorable influence of the treatment with the above-mentioned mixture, a group of 121 patients were chosen for study using this mixture. The purpose of this paper is to report the progress of these studies.

This study differs from those of other observers[1,2,6] using combined antigen-antihistamine agents in that an injectable solution of Chlor-Trimeton Maleate was combined with allergenic extracts, and no other form or dosage was used other than that to be described.

METHODS AND MATERIALS

Two to 4 mg and rarely more, of Chlor-Trimeton Maleate in solution were added to the syringe containing the antigen used in the desensitization process, and the two were injected simultaneously under the skin.

A total of 121 patients were studied (as shown in Table I) with a history of allergy or sensitivity to pollens, dust, or molds demonstrated by test.

TABLE I.

Type of Sensitivity	Total No. Cases
Seasonal Allergic Rhinitis (Tree Pollen)	10
Seasonal Allergic Rhinitis (Grass Pollen)	17
Seasonal Allergic Rhinitis (Ragweed Pollen)	28
Seasonal Allergic Rhinitis (Tree, Grass, Ragweed, Plantain)	35
Perennial Allergic Rhinitis and Seasonal Rhinitis (Pollen and Dust or Molds)	10
Perennial Allergic Rhinitis (House Dust and Molds)	21
Total Cases	121

All patients observed in this study were seen at least once weekly and in some instances twice weekly. Patients were specifically instructed to observe the size of local reactions, if any, and to report any symptoms or

Doctor Silbert is Chief of Allergy, Captain John Adams Hospital, Lawrence Quigley Memorial Hospital and Soldier's Home, Chelsea, Massachusetts; Consultant in Allergy, Danvers State Hospital, Danvers, Massachusetts; Junior physician and assistant in the Department of Allergy, Mount Auburn Hospital, Cambridge, Massachusetts.

The Chlor-Trimeton Maleate Injection was furnished by Dr. M. William Amster, Medical Service Department, Schering Corporation, Bloomfield, New Jersey.

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constitutional reactions. With each visit the subjective complaints and the local reactions were recorded.

RESULTS

During treatment the previous years, small doses of pollen extract given alone produced side effects varying in intensity from moderately severe local reactions to constitutional reactions in twenty-eight hypersensitive patients in the group. The severity of the reaction or the patient's reluctance to continue caused therapy to be abandoned in some cases. Five of the twenty-eight were "constitutional reactors." In 1950, they consented to accept treatment with the new technique, namely, the subcutaneous administration of combined antigen-antihistamine. Eight refused therapy for 1950.

The remaining fifteen hypersensitive patients took the combined therapy with a markedly reduced incidence of side effects. These patients were able to tolerate larger doses of antigen; in many instances, doses were given which were weeks in advance of the previous year's chronological dosage. Such phenomena were repeatedly observed. However, most interesting was the observation that the five "constitutional reactors" could tolerate large doses of antigen when combined with Chlor-Trimeton. Comparison of the doses of antigen alone causing a reaction with those the patients were able to tolerate when administered simultaneously with an antihistamine, as well as the total dosages received during the 1950 season, may be seen in Table II. With the combined therapy these patients completed the season with a minimum of symptoms of hay fever or of hay fever with asthma. Patient No. 3 also completed the 1951 tree season with a minimum of hay fever symptoms. Patient No. 1 finished treatment symptom free. Patient No. 2 finished treatment with a minimum of hay fever. Patient No. 4 finished treatment with no asthma and only a minimum of symptoms. Patient No. 5 finished the season symptom free.

DISCUSSION

Treatment was commenced in the other ninety-three patients on the basis of tests with various dilutions of pollen extracts and miscellaneous allergens. A number showed marked sensitivity to pollen extracts and house dust. It was suspected, therefore, that they might become reactors if treated in the conventional manner. However, all except six completed their treatment with combined antigen-antihistamine injections with no side reactions. Four of the six had moderately severe reactions; two had constitutional reactions, in the higher dosage levels.

In keeping with traditional ideas in the treatment of allergic disease by desensitization, a local reaction exceeding the size of a silver dollar necessitates a cautious return to the last dose of antigen producing no larger a local reaction. It must be stressed that in this study deliberately increased amounts of antigen, when combined with Chlor-Trimeton, produced minimal local reactions, or none at all, whereas the antigen given alone might

TABLE II.

Patient	Type of Sensitivity; Diagnosis	Type of Reaction	Single N.P.U. dose causing a reaction during treatment in 1949	Single N.P.U. dose patient tolerated in 1950 combined with Chlor-Trimeton Maleate	Total N.P.U. dose patient received in 1950 with Chlor-Trimeton Maleate
1	Ragweed Pollen; Hay Fever	Severe to constitutional	80	4000	23,000
2	Ragweed Pollen; Hay Fever	Severe to constitutional	500	5000	22,500
3	Tree Pollen; Hay Fever	Constitutional	350	5500	27,000
4	Dust and Ragweed Pollen; Hay Fever and Asthma	Constitutional	200	5500	24,000
5	Grass and Ragweed Pollen; Hay Fever and Asthma	Moderately severe to constitutional	250	5200	27,000

N.P.U.—Noon Pollen Unit

well have produced constitutional reactions. It is felt that with the increased amounts of antigen thus possible, a higher neutralizing antibody titer is produced.

In twenty-three patients it had not been possible, because of reactions, to administer an adequate dosage of antigen to stimulate antibodies and confer immunity. The patients, therefore, failed to experience a fully adequate measure of relief. During 1950 with Chlor-Trimeton Maleate, the Noon Pollen Unit dose was increased at each visit beyond that of the previous year and without reactions. Sometimes double or even triple doses were given. By the end of the treatment schedule these patients had received an average total dosage of 29,000 N.P.U.

It was thought that if the antigen could be raised to the highest level of tolerance, sufficient neutralizing antibody would be produced. Kabat[4] and others consider this a contentious theory. However, judging by the excellent clinical results obtained by using the combined method of therapy, further study and confirmation would seem to be indicated.

The study with Chlor-Trimeton was undertaken with the thought that admixture of an antihistamine with the antigen might decrease the production of histamine-like substance, possibly counteract some of it, and at the same time increase the formation of protective antibodies. When the antibodies in hypersensitive individuals come in contact with their specific antigens, unbound histamine is released; the administration of an antihistamine is believed to prevent local and general reactions because of a reduction in capillary permeability that prevents the spread of injected antigens that otherwise might occur. This belief is supported by the work of Vallery-Radot and his co-workers, whose studies on the mechanism of action of antihistamines indicate that these drugs act primarily on the vascular wall, altering its permeability.[10] As expected, it soon was observed during treatment that patients in whom small doses of antigen previously produced large local or even constitutional reactions were able to receive measurably larger doses of the same antigen when combined with injectable Chlor-Trimeton.

Furthermore, there is reason to believe that the increased antibody and immunizing titer may stimulate the production of ACTH so that subsequently there occurs indirectly a decrease in circulating eosinophils and an increase in the production of histaminase, the enzyme which neutralizes histamine, with resultant diminution in the symptom complex of allergic disease.

Long and Favour[5] observed that, when ACTH was present in normal or excessive quantities, the whealing reaction of the polysaccharide test on patients who had had pneumococcic pneumonia failed to develop, which may be interpreted to mean that the histamine-like substance in the skin had been neutralized. Rose[7] of McGill University, in a personal communication, says that "another way of looking at it is that the administration of ACTH in this case prevents antibody formation, and therefore no skin reaction occurs; but that is open to question."

Horton[3] states: "For some strange reason the whole (adrenal) cortical extract seems to reduce the patient's sensitivity to histamine." This may well be explained by the remarks just made.

Rose[8] has demonstrated the inhibition of histamine and the fall in the blood plasma level when an antihistamine is used. This is amply confirmed in the present study with Chlor-Trimeton.

CONCLUSION

1. One hundred and twenty-one patients with perennial or seasonal rhinitis received injections of a combination of Chlor-Trimeton Maleate and allergenic extracts.

2. This group of patients required fewer treatments than those treated in the conventional manner.

3. The final dose of extract or extracts was considerably higher in the patients receiving the combined therapy.

4. Constitutional as well as large local reactions were markedly reduced in the group receiving combined therapy.

5. Treatment with combined therapy appeared to increase the number of successfully managed cases and is a valuable method, especially in those patients in whom increments in allergenic doses may give rise to serious reactions.

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214 Ocean Street

TREATMENT OF BRONCHIAL CONDITIONS WITH A COMBINATION OF ANTICHOLINERGIC, ADRENERGIC, AND ANTIHISTAMINIC DRUGS

Preliminary Report

NATHAN E. SILBERT, M.D., F.A.C.A.

Lynn, Massachusetts

THE concept that bronchial asthma may be a result of parasympathetic stimulation ("pathologic vagotonia") was proposed by Eppinger and Hess[2,3] in 1909. They theorized that the liberated acetylcholine acts upon the bronchial musculature and submucosa of the asthmatic patient, producing bronchial edema and muscular constriction with resultant bronchospasm and an attack of asthma. If this is so, then drugs which inhibit the action of cholinergic nerves, such as belladonna alkaloids, should be effective in bronchial asthma. Loeffler[5] found this so when, in 1924, he reported good results in the treatment of bronchial asthma with the use of levorotatory belladonna alkaloids. Beakey et al[1] demonstrated that levorotatory belladonna alkaloids protected against the bronchospastic effects of acetyl-B-methylcholine but had no effect on the bronchospasm produced by histamine.

The author, on the basis of previous studies[8] and observations made by Feingold[4] in his discussion of bronchial conditions and the theory of reversible tissue change, postulates that:

1. Asthma,[6] which previously has been defined as intrinsic asthma, actually is an alveolar damage with pathologic dysfunction, and probably overactivity of the cholinergic system and resulting in irreversible change.
2. Extrinsic asthma is functional change in alveolar structure with bronchospasm and the release of unbound cellular histamine, but without alveolar damage, and producing a reversible change. Repeated and protracted episodes of this functional alveolar change may result in bronchiole damage, and thus lead to pathologic dysfunction or intrinsic asthma.
3. Continued failure of the alveolar structure (shock organ) to withstand excessive stress and strain[7] may result in emotional asthmatic seizures, functional alveolar change, or pathologic alveolar change.

These theories, along with the quoted findings and a review of the literature on the use of levorotatory alkaloids of belladonna, suggested a study of anticholinergic and adrenergic drugs combined with antihistamines in the control of chronic asthmatic bronchitis, chronic bronchitis, and allied bronchospastic conditions.

Initially, the levorotatory belladonna alkaloid in the form of Belladenal Elixir* was used alone. Later, potassium iodide was added for its liquefying effect on inspissated mucus and for counteracting the drying action of belladonna alkaloids on the mucous membranes of the tracheobronchial

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TABLE I. TOTAL NUMBER OF CASES: 25

Diagnosis	No. Cases	Symptoms (all 3 groups of patients might present any one or any combination of the symptoms described)	Belladenal (alone)	Belladenal with Potassium Iodide and Ephedrine Sulfate	Belladenal Placebo	Syrup of Phenergan with Belladenal, Potassium Iodide, and Ephedrine Sulfate	% Cases Relieved
Chronic bronchitis with or without emphysema	12	Shortness of breath. Coughing. Raising. Abdominal breathing. Occasional harsh ronchi. Prolonged expiration with feeble breath sounds. Decreased vital capacity.	No appreciable change.	Decrease of coughing, shortness of breath. Moderate increase of vital capacity. Sputum more liquid. Less inspissated mucus.	Return of original symptoms.	Decrease of coughing, and shortness of breath. Moderate increase of vital capacity. Sputum more liquid. Less inspissated mucus.	10—83%
Chronic bronchitis with bronchial asthma—cause undetermined	7	Same as above with occasional evidence of cyanosis. Right heart embarrassment. Some chest deformity. Some feeble breath sounds.	No appreciable change.	Decrease in expiration time. Increased breath sounds. Less dyspnea.	Return of original symptoms.	Decrease in expiration time. Increased breath sounds. Less dyspnea.	5—71%
Allergic asthmatic bronchitis—cause determined by diagnostic tests	6	Paroxysmal dyspnea with wheezing, coughing, and tightness in chest. Expiratory dyspnea.	No appreciable change.	Decrease in wheezing. Less choking.	Return of original symptoms.	Marked decrease in wheezing and choking.	5—83%

tree, which, next to the bronchospasm, is the most annoying symptom of bronchitis and asthma. Ephedrine was chosen as an ingredient of the mixture to assist in relieving the bronchospasm and to overcome the sedative action of the parasympatholytic alkaloids. Finally, an antihistamine, Syrup of Phenergan** was added to the combination to combat those factors in asthma which might be due to the excessive release of unbound histamine in the alveoli not overcome by belladonna alkaloids alone. In cases of allergic bronchitis, it was observed that the addition of Syrup of Phenergan produced a more efficient and faster acting medicament.

Clinic patients together with those from the author's private practice served as the study group. Twenty-five such subjects with asthma or chronic bronchitis with emphysema and/or wheezing received Belladenal Elixir. Fair results with some relief of the bronchospasm were obtained with this medication alone.

When potassium iodide was added to the Belladenal, the dry barking cough changed to a loose one, and instead of raising thick inspissated mucus, patients now raised more fluid sputum and were able to do so with relative ease. The wheezing, however, did not appreciably change.

*Elixir of Belladenal was supplied through the courtesy of C. Henze, M.D., Medical Director, Sandoz Pharmaceuticals, New York City.

**Syrup of Phenergan was supplied through the courtesy of Wyeth, Inc., Philadelphia.

Fifteen of the twenty-five patients were selected for testing the effect of adding ephedrine sulfate to the mixture containing Belladenal and potassium iodide. A gratifying change occurred. Mucus became more liquid and the raising of it was further facilitated. Wheezing lessened in some patients and stopped in others. In order to gauge the effectiveness of the combination, placebo medication was substituted in ten of the fifteen patients. Within forty-eight hours, eight patients reverted to their previous status before any medication had been given, and no improvement whatsoever was apparent. After one week, the mixture of Belladenal, potassium iodide, and ephedrine sulfate was readministered; improvement again became apparent. After the initial mucus plugs had been raised, coughing eased considerably and the amount of secretion decreased. Patients who produced from 1/4 to 2 cups of sputum daily produced after medication 1 to 3 teaspoonfuls daily, usually early in the morning. Further observation revealed that it was possible to decrease the amount of adjunctive sedative medication these patients were receiving. Results in these twenty-five patients are shown in Table I.

Extending the experiment to include an antihistamine with the levorotatory belladonna alkaloids, the following combination was derived:

Antihistamine (Syrup of Phenergan)	ozs. ii	60cc
Ephedrine Sulfate	grs. x	or 0.65 gm.
Saturated Solution Potassium Iodide	ozs. ss	15 cc
Belladenal Elixir q.s. ad	ozs. vi	180 cc

The study group included:

	No. Patients
Chronic bronchitis with or without emphysema	30
Chronic bronchitis with bronchial asthma	12
Allergic asthmatic bronchitis	29
Total	71

A total of seventy-one patients received this combination, among them forty-two males and twenty-nine females, varying in age limits from one and one half to seventy-nine years. Of the seven children in the group, two girls were aged three and ten years, and five boys ranged in age from one and one half to fourteen years. Diagnoses were confirmed by laboratory studies, x-ray findings, and diagnostic allergic tests.

The twelve patients with chronic bronchitis and in addition the complete syndrome of bronchial asthma, who on skin tests failed to show any definitely positive allergens, were considered cases of intrinsic asthma or alveolar pathologic dysfunction. The diagnosis of allergic asthmatic bronchitis was proven by diagnostic allergic studies and confirmed by history and laboratory work-up. Eight of this group of twenty-nine had combined dust and mold positive allergens, together with pollen asthma; the asthma was perennial in nature but more severe during the pollinating season. The remaining twenty-one patients had a miscellaneous group of positive allergens resulting in either seasonal or perennial episodes and seizures of bronchial asthma.

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TABLE II. TOTAL NUMBER OF CASES: 71

Result	Breathing (Asthmatic Syndrome)	Coughing	Sputum	No. Cases	%
Excellent relief	Normal	Minimum	Minimum	24	33
Good Improvement	Relatively normal	Greatly reduced	Minimum	31	43
Fair relief	With some difficulty	Some improvement	Partly reduced	10	14
No improvement	Wheezing & dyspnea	No change	Thick; no reduction	6	8

The seventy-one patients received doses of the combined admixture varying according to age from 1/2 to 2 teaspoonfuls every four to six hours and at bedtime. Both children and adults tolerated the mixture well. Gratifying results were obtained and coughing was reduced to a minimum. Patients with chronic allergic asthmatic bronchitis responded particularly well, even those patients who had had symptoms for periods up to twenty years. Some of the patients who had been residents of a domiciliary institution as long as twenty years stated that they were breathing much more freely than they had done in several years. The number of patients in the entire group experiencing relief of symptoms of asthma and bronchitis far exceeded the author's expectations. Table II shows the results.

IMPRESSION AND CONCLUSION

A preliminary study of levorotatory belladonna alkaloids combined with an antihistamine, ephedrine sulfate, and potassium iodide has shown that:

1. This combination represents an advance in the treatment of chronic bronchitis.
2. The combination was effective in patients of all age groups.
3. The most striking effect was observed in those patients in whom tenacious inspissated mucus, wheezing, and hacking coughs were the cardinal symptoms.
4. The addition of Syrup of Phenergan to the combination made it more effective, particularly in allergic asthmatic bronchitis.

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214 Ocean Street

MULTIPLE ANTIHISTAMINE THERAPY

Preliminary Investigation

NORMAN SHURE, M.D., F.A.C.A., JEROME J. SIEVERS, M.D.,
and M. COLEMAN HARRIS, M.D., F.A.C.A.
Los Angeles, California

ANTIHISTAMINES have proved to be valuable adjuncts in the management of some forms of allergic disease. Their oral administration often provides rapid and dramatic relief of symptoms in urticarial dermatoses and in hay fever; they are less effective in perennial allergic rhinitis and atopic dermatitis, and are of little if any value in asthma. In clinical practice, however, the usefulness of this class of drugs has been mitigated by two important factors: (1) the frequent occurrence of undesirable side effects, and (2) the wide variation in individual therapeutic response. Both of these factors are to some extent unpredictable. Some patients will tolerate without difficulty an antihistamine which in others causes undesirable side effects. Furthermore, one drug will produce good results in some patients and poor results in others. Therefore, the physician must try one antihistamine after another before finding one, which for the particular patient will give good results without undesirable side effects. In making his selection he must choose from a list of some fifty to sixty drugs, all with different names and many of identical chemical composition. This is time consuming, costly, and often confusing. Any means which would tend to minimize these difficulties would seem worthy of trial.

Antihistamines have been administered in combination with other classes of drugs, some to enhance their action, others to counteract side effects. Hubbard and Berger[1] studied the therapeutic efficiency and incidence of undesirable side reactions of a combination of two antihistamines, one through to be soporific and the other stimulating. Their results were inconclusive, with the incidence of symptomatic relief somewhat enhanced but the frequency of side reactions more or less unchanged.

All of these combinations utilized full therapeutic doses of the antihistamine and have not overcome the basic difficulty of antihistamine therapy, the unpredictable therapeutic response and undesirable side effects. We decided, therefore, to study the action of a mixture of antihistamines, each in a dose smaller than commonly used. This would have the effect of trying several drugs at one time and thus, to some extent, reduce the time required to find the effective drug for the particular patient. Furthermore, the reduced dose of each antihistamine could conceivably result in a lower incidence of side effects, and yet the total doses in the combination could be sufficient to produce adequate therapeutic response,

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From the College of Medical Evangelists, School of Medicine and the White Memorial Hospital, Los Angeles.
Dr. Harris's present address is The Permanente Foundation, Vallejo, California.
Approved for publication June 23, 1952.

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TABLE I. CLINICAL RESULTS WITH TRI-HISTIN

Diagnosis	Trials	Excellent		Good		Poor		Total Improved	
		No.	%	No.	%	No.	%	No.	%
Allergic Rhinitis	84	52	61.19	8	9.5	24	28.6	60	71.5
Chronic Urticaria	4	2	50.0	1	25.0	1	25.0	3	75
Bronchial Asthma	62	4	6.5	10	16.3	48	77.4	14	22.8
Eczema	6	2	33.3	0	0	4	66.7	2	33.3
Questionable Allergic States	2	0	0	0	0	2	100.0	0	0

TABLE II. CLINICAL RESULTS WITH PLACEBO

Diagnosis	Trials	Excellent		Good		Poor		Total Improved	
		No.	%	No.	%	No.	%	No.	%
Allergic Rhinitis	68	5	7.4	5	7.4	58	85.3	10	14.7
Chronic Urticaria	5	0	0	1	20	4	80	1	20
Bronchial Asthma	18	1	5.5	1	5.5	16	88.9	2	11.1
Eczema	4	0	0	0	0	4	100	0	0
Questionable Allergic States	3	1	33.3	0	0	2	66.6	1	33.3

For the purposes of this study, the compound Tri-Histin* was chosen. This preparation is a combination of three antihistamines in equimolecular proportions so that each 50 mg tablet contains 20 mg of chlorothenyl pyramine citrate (Chlorothen or Tagathen), 13 mg of thenylpyramine hydrochloride (Thenylene or Histadyl 17 mg of pyrilamine maleate (Neo-Antergan). This compound was studied by (a) clinical trial and (b) quantitative bioassay.

CLINICAL TRIAL

Patients with common allergic conditions under treatment at the Allergy Clinic were chosen for this study. These were patients who had not received relief from the trial of several antihistamines or had been unable to take them because of undesirable side effects. In order to minimize the emotional component among the patients and to eliminate any personal bias among the physicians participating in the study, the antihistamine combination in tablet form and identical appearing tablets of placebo were each placed in individual packets, and the packets numbered by a code. The packets were then dispensed at random with instructions to the patient to take one tablet three times a day and to report the results in one week. Some patients, during the course of the several weeks the study was in effect, took the antihistamine one week and the placebo another. Others took only the drug, while still others took only the placebo. The entire study was as objective as possible; the dispensing physicians were thoroughly unaware of the code, merely recording the results on the patient's record.

The results of the clinical study are shown in Tables I and II. There were 171 patients involved in this study, representing 256 individual trials of the drug or placebo. In cases of allergic rhinitis sixty of eighty-four

*An adequate supply of Tri-Histin was generously supplied for this study by Andrew A. Recsei, Ph.D., of The Recsei Laboratories, Santa Barbara, California.

TABLE III. INCIDENCE OF SIDE EFFECTS

Diagnosis	Tri-Histin			Placebo		
	Trials	Side Effects	%	Trials	Side Effects	%
Allergic Rhinitis	84	7	8.3	68	6	8.8
Chronic Urticaria	4	0	0	5	0	0
Bronchial Asthma	62	7	11.3	18	2	11.1
Eczema	6	0	0	4	0	0
Questionable Allergic States	2	0	0	3	0	0

patients (71.5 per cent) were improved with the antihistamines, while ten of sixty-eight patients (14.7 per cent) reported relief of symptoms from the placebo. In chronic urticaria three of four patients (75.0 per cent) reported temporary clearing of their lesions from Tri-Histin, and only one of five (20.0 per cent) was benefited from the placebo. In bronchial asthma fourteen out of sixty-two patients (22.8 per cent) claimed relief of symptoms after taking the antihistamine; two out of eighteen patients (11.1 per cent) noted improvement after taking the placebo. In eczema two of six patients (33.3 per cent) were relieved of their itching with the drug, while none noticed any difference in their symptoms while taking the placebo. The miscellaneous grouping in "Questionable Allergic States" included one patient with an idiopathic headache, one with purpura, and one with vague gastrointestinal symptoms. In this group none of the patients was relieved with the antihistamine, while one patient (headache) was improved after taking the placebo.

The incidence of undesirable side effects is shown in Table III. In our series the percentage of side reactions was, on the whole, small, being 8.3 per cent in allergic rhinitis, none in chronic urticaria, 11.3 per cent in bronchial asthma, none in eczema, and none in the questionable allergic states. The incidence of side reactions occurring in patients taking the antihistamine combination was not significantly different from that in those taking the placebo. Furthermore, the side effects reported by most of our patients were not the common ones of drowsiness, dryness of the mouth, excitability, and palpitation. They were vague symptoms like "feverish feeling," "butterflies in the stomach," and "weakness of the knees."

QUANTITATIVE BIOASSAY STUDIES

It has been shown[3] that the power to inhibit a histamine-induced wheal is an accurate and comparatively simple method of assaying the activity of antihistamines. This is done by determining what strength of antihistamine solution will inhibit the flare produced by a known dilution of histamine. We found that a 0.275 mg per cc solution of histamine diphosphate, representing 0.1 mg per cc of histamine base (1:10,000), produced the most constant and easily measurable flare. The dilutions of antihistamines we found adaptable ranged from 1:500 to 1:80,000.

Parallel rows of identical scarifications were made with a standard

Broadbent scarifier on the backs of selected subjects. On the first row of abrasions drops of distilled water were applied as a control. On the abrasions in the other rows, various dilutions of the antihistamines, Tri-Histin, Thenylene, Clorothen, and Neo-Antergan were placed. After ten minutes, the drops of water and antihistamine solutions were wiped off with care so as not to contaminate the individual sites. On each site so prepared, a drop of histamine solution (1:10,000) was then placed, and any resulting flare was traced with a ball point pen and transferred to the adhesive side of a strip of transparent cellophane tape. This study was repeated on fourteen individuals who had previously been found to respond to this dilution of histamine solution with a good measurable flare.

A typical response is reproduced in Figure 1. In the highest concentration of the antihistamines, 1:500, all of the histamine-induced wheals were successfully inhibited. In the lowest concentration, 1:80,000, none of the antihistamine solutions were successful in inhibiting the histamine reaction. In the Thenylene row a flare begins to appear in the 1:5,000 site, becoming progressively larger as the concentration of the antihistamine solution diminishes. Similarly, in the row of abrasions pretreated with Chlorothen, the flare is apparent in the 1:10,000 site and becomes more pronounced with successively lower concentrations. Neo-Antergan successfully inhibits the histamine flare through a dilution of 1:10,000, while Tri-Histin allows the appearance of a flare in the 1:20,000 concentration, with a somewhat slower loss of inhibitory powers as the dilution is increased.

The relative efficiency of Neo-Antergan, Thenylene, and Chlorothen, on the basis of their powers to inhibit a histamine-induced flare as found in this study, corresponds with the results found by others using this method of bioassay. The interesting finding in this study, however, is the apparent efficiency of Tri-Histin. It must be remembered that Tri-Histin is a composite drug containing one third each of the three other antihistamines studied. Thus in a 1:20,000 solution of Tri-Histin the concentration of each of its three ingredients (Neo-Antergan, Chlorothen, Thenylene) is not greater than 1:60,000.

DISCUSSION

In any study of the therapeutic efficacy of antihistamines, one must constantly keep in mind the uncontrollable variables which are likely to alter the results of the study. Among the most obvious of these are the constantly changing allergic atmosphere of the individuals being studied, the great variation in symptom threshold of the patients, the effect of additional treatment being given, the normal cyclic variations of allergic symptoms, and the emotional status of the patient. Obviously, there does not exist any method of clinical study which can be controlled perfectly. Furthermore, it is very apparent that comparison of results obtained in one segment of the country with that of another is hardly accurate.

In spite of all these drawbacks, we feel that several conclusions are sug-

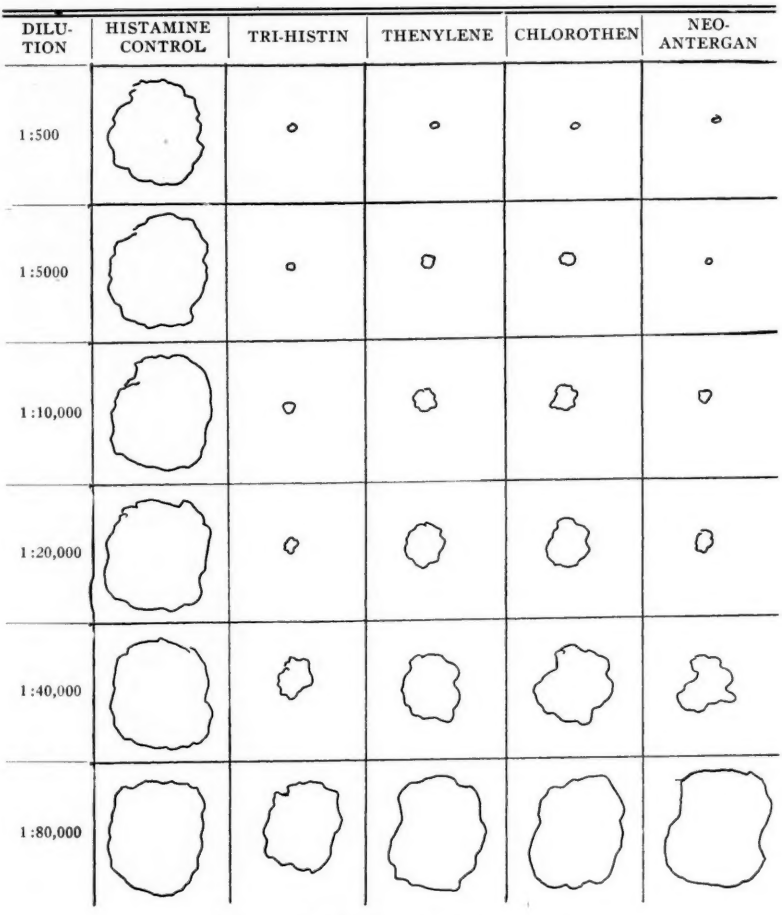

Fig. 1. Histamine wheal inhibition tests.

gested and are justified by the results of this study. It must be remembered, first, that the subjects in this group were those who had taken other antihistamines previously without success. Second, the method of controlling the study with the use of placebos was as unbiased as is possible. Third, the patients participating were of a homogenous group under identical conditions. We can only conclude, therefore, that the mixture of three antihistamines, as used in this study, is as effective or perhaps more effective than a much larger dose of only one. Further, the undesirable side effects following the administration of the mixture containing small amounts of three antihistaminics are much less than are experienced from the use of a large dose of one.

These results suggest that there is a synergistic action present with the use of small amounts of three antihistamines. This appears to be corroborated by our bioassay studies which indicate that Tri-Histin, a mixture of three antihistamines, is more effective in inhibiting a histamine-induced wheal than is any one of its three components.

SUMMARY

A combination of three antihistamines, each in a dose approximately one third the average dose, was studied by clinical trial and by quantitative bioassay. Good to excellent relief was reported by 71.5 per cent of the patients with allergic rhinitis, 22.8 per cent of those with asthma, 75 per cent with chronic urticaria, and 33.3 per cent with eczema. This is compared to relief obtained after the use of a placebo: 14.7 per cent with rhinitis, 11.1 per cent with asthma, 20 per cent with urticaria, and 0 per cent with eczema. The incidence of side effects was minimal and was the same in both groups.

Histamine-induced wheals were inhibited by the combination of antihistamines in a dilution greater than that of any single component of the mixture. A synergistic action is suggested.

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Both pamphlets are available, free of charge, from the Department of Public Relations, American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

THE USE OF CHLOR-TRIMETON IN ALLERGIC DISEASES, WITH SPECIAL REFERENCE TO ITS INJECTABLE ADMINISTRATION

CLARENCE BERNSTEIN, M.D., F.A.C.A., and
SOLOMON D. KLOTZ, M.D.

Orlando, Florida

THE use of histaminolytic agents as adjuvants in the therapy of allergic disorders, such as perennial and seasonal rhinitis, acute and chronic urticaria, angioedema, drug eruptions, atopic dermatitis and other conditions, has become well established. A series of some twenty or more antihistamines has been introduced since 1945. The problem then is to choose the agent most suited to the needs of the average patient. Desirable features of an antihistamine include (1) safety, (2) clinical effectiveness, (3) long duration of action, and (4) maximum freedom from undesirable side effects. It has been our object to study the most promising antihistamines as they have appeared. The present report deals with Chlor-Trimeton®* (CTM), one of the newer compounds. This drug has been available to us since its development. Our experience includes the use of regular 4 mg tablets, a "repeat action" tablet of 8 mg, and a parenteral preparation containing 2 mg/cc.

CLINICAL STUDIES

Published reports[2-7,9] have shown that this drug provides substantial to complete relief of symptoms in the majority of patients with hay fever, perennial allergic rhinitis, acute or chronic urticaria, and angioedema. Considerable benefit has been obtained in some cases of extrinsic (pollen) asthma, and in atopic dermatitis or atopic eczema. The incidence of side reactions reported ranged between 3 per cent and 14 per cent. Most investigators commented on the mild nature of side effects noted.

Acute and chronic toxicity studies in laboratory animals (dog, rat) have failed to show any abnormality in the blood picture or in the heart, lung, liver, spleen, kidney, or adrenals at autopsy following prolonged oral administration of 2 mg/kg of body weight. This is further borne out in our clinical experience in which patients on CTM for over four years have shown no untoward effects.

We have used Chlor-Trimeton tablets both in the 4 mg doses and in the 8 mg size (repeater type) in 658 cases embracing most of the clinical allergic entities, such as hay fever, vasomotor rhinitis, allergic asthmatic bronchitis with or without nasal or ocular manifestations, atopic eczema, allergic neurodermatitis, pollen dermatitis, poison oak-ivy eczema, migraine of allergic origin, urticaria, and angioneurotic edema.

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*Chlor-Trimeton Maleate is 1-(p-chlorophenyl)-1 (2-pyridyl)-3-N, N-dimethylpropylamine maleate and was supplied by Schering Corporation, Bloomfield, New Jersey.

The repeat action tablets are designed to have both an immediate and a delayed action. An outer coating contains 4 mg of Chlor-Trimeton which is immediately available upon ingestion of the tablet, thus providing an initial dose of antihistamine. A second 4 mg dose of the medication is contained in an inner core separated from the outer coating by the middle layer, which disintegrates four to six hours after ingestion of the tablet.

Our experience confirms that of other investigators. CTM yielded relief in approximately 85 per cent of these cases. It was important to note that it held the symptoms in check while etiological factors were sought out and, when found, removed. Five per cent of the patients received no benefit or thought the drug disagreed, and 10 per cent received inconstant relief. Eleven patients could not take the drug because of one or more of the following complaints: nausea, gastric irritation, headache, general malaise, drowsiness, nervousness, excitability, or increased sweating. In none of our cases were unfavorable changes in the blood noted. The least effective results were in asthma and headache; the most effective in hay fever, vasomotor rhinitis, angioedema, and urticaria. The drug is also helpful in those individuals susceptible to mosquito and other insect bites. Children tolerated relatively larger doses than adults, and the 8 mg tablet, when given in the morning, keeps symptoms under control until after school. Likewise it keeps the upper airway comfortable from retiring hour until waking. Occasionally an early afternoon dose may be required to give full twenty-four-hour "coverage." The only disadvantage of the repeat action tablet is seen where the patient tolerates the 2 mg dose only, in which event the delayed action must be sacrificed.

We have found CTM helpful in one or two other situations. Occasionally the child with a sensitive upper respiratory tract enjoys swimming but finds the water or the chilling or both are irritating to the mucous membranes. A prophylactic dose of CTM thirty minutes before immersion often prevents the usual unpleasant sequelae. The individual who cannot eat shrimp, or who must attend a party where interdicted foods may be served, can often be spared "paying the allergy piper" by taking his medication thirty minutes to an hour before the anticipated meal. The occasional allergic patient who gets air-sick or "air-ears" has been afforded a more pleasant plane trip for having used CTM anticipatorily. For suspected allergic headaches, particularly those with sinus reference of pain, Coricidin (PAC plus CTM) has proved useful in both relief and prevention.

CTM INJECTABLE

We have had a somewhat more limited experience with Chlor-Trimeton injectable. This preparation was supplied us in a water solution 2 mg/cc at a pH of approximately 5.0. In 326 patients representing more than 1000 injections, we have confirmed all the beneficial effects seen from

oral administration but usually with more immediacy of action. The intravenous route was used often enough to be certain that in a 1.0 to 2.0 cc dosage, depending on the weight of the patient and the severity of the clinical condition, no untoward reactions occurred, indeed even less than would have been anticipated from physiologic saline solution in normal controls. An occasional patient reported slight dizziness or nervousness and, at times, dryness of the mouth, but there were no reactions of enough moment to withhold repeat injections.

The most common use made of this material was as an adjunct to hyposensitization therapy where overdosage was considered possible, or where symptoms were present at the time of injection. Subcutaneously the medication stung or smarted for a bit, but offered no other objectionable feature and did allow us to raise the treatment dosages higher and more rapidly than otherwise could have been done. In some instances the pollen solution and the medication were mixed and then injected, but this was not the usual practice. One disadvantage, however, is the reduction in the erythema-swelling reaction so often useful as a guide to the next future dose in therapy, but this has proved no drawback in actual practice.

It is in the weeping dermatoses and urticarias that we have seen the most dramatic short-term relief. Hitherto we could only give calcium gluconate by vein and hope for some subjective, if not objective, improvement. After the injection of CTM, however, the hives visibly disappear, and the weeping eczemas appreciably reduce their exudate almost before the needle is withdrawn from the vein. The patient reports subjective relief as well. It appears thus far that the calcium and the CTM potentiate one another, and together are superior to either alone; hence we commonly mix them in the same syringe and administer them together. In either method it must be stressed that only temporary, short-lived improvement can be offered, but the remedial effects can be obtained and injections repeated whenever needed for acute exacerbations or recurrences.

The dose of CTM used ranges from 0.4 to 2.0 cc by vein, and subcutaneously from 0.5 to 1.0 cc. The latter doses by the subcutaneous route are smaller because of the "bite" or smarting from the injection complained of by the patient.

A further use that appears important is in the prevention of some untoward drug reactions, specially the histamine type. By giving 0.5 cc i.v. prior to the injection and followed immediately by the drug desired, we have succeeded in blocking some of the regularly encountered disturbing reactions. Likewise, with Demerol® and opiates, we find that in many patients the injection of CTM prevents or greatly moderates the nausea following these drugs.

In a very few cases, we have permitted the use of this material for relief of tensional states, including headache, but our experience has been too limited to permit more than the thought that it may be helpful. This is

probably due not only to its mildly sedative effect (for most individuals) but to the mental suggestion offered by hypodermic therapy.

COMMENT

The exhibition of charts and graphs and the recitation of individual case histories would add little of real worth to this report. The control observations were more than adequate by virtue of experience during the previous season in many instances, prior therapeutic efforts with related pharmaceuticals in others, and, as regards the injectable, by direct comparison with a similar and very useful material supplied by another manufacturer (to be reported later).

Lest this account be considered intemperately optimistic, we wish to stress that the antihistamines, while very useful, have not solved the riddle of clinical allergy, any more than did epinephrine and ephedrine before them, nor ACTH and cortisone after them. One still must use the disciplines and training of the well-oriented allergist and bring to bear on every problem the careful scrutiny and examination of the well-grounded physician.

Concerning the antihistamines, and they are quite helpful therapeutically, we have had a rather full experience with CTM which we report herewith. In a few instances, we found that one of the others seemed to fit the patient slightly better or we had to change from one to another in the same individual. Each patient was a lock for which an antihistamine key was sought. CTM seemed to fit more of them. There is, however, no "master key" as yet.

With all the help gained from these newer advances, we still find that we must generally resort to "specific" methods to gain the best ultimate results. Hyposensitization therapy or successful avoidance of the allergenic offenders lead to the best long-term therapeutic victories. In this latter regimen, the antihistamines offer a genuine adjunct to successful treatment.

CONCLUSION

Chlor-Trimeton Maleate has proved to be a potent antihistamine, therapeutically most effective in vasomotor rhinitis, hay fever, urticaria, and angioneurotic edema.

Our most recent experience with CTM injectable opens a wide range of clinical usefulness where more rapid antihistaminic effects are desired or the condition of the patient precludes medication by the oral route.

In the prevention of allergic and drug reactions, in the treatment of urticarias, especially some of them from penicillin sensitivity, and in the relief of weeping eczemas, the intravenous administration of CTM has been most effective, at times dramatic.

The paucity of untoward side effects and the wide range of therapeutic

effectiveness justify further and continued use of CTM in the treatment of allergic and related diseases.

It is important to bear in mind, however, that the antihistamines as a whole are but one of the modalities of antiallergic therapy. Treatment must still be based on accurate diagnosis wherever possible and directed by sound clinical judgment.

ADDENDUM

Since submitting this report for publication we have had two sun-sensitive patients made able to enjoy the beach without protection from the sun other than CTM repeater tablet taken prophylactically thirty minutes to one hour prior to exposure.

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740 North Magnolia Avenue

PSYCHOLOGICAL FACTORS IN STATISTICAL EVALUATION

In ten rheumatism clinics patients suffering from fibrositis were treated with Adrenalin cream, and with a similar cream which contained no Adrenalin. None of the investogators knew which of the creams contained Adrenalin. Each cream was massaged into one or two painful areas for five minutes. The effects were measured after five minutes, thirty minutes and one week later. When the patient attended the clinic the second week, the sites and inunction of the two creams were reversed.

Some observers reported consistently better reports with both creams than with others, but in any case, of the thirty-nine patients treated, 29 per cent reported improvement with the Adrenalin cream and 25 per cent with the inert cream.—Waters, E. G. L.: Comparative therapeutic value of massage with "Adrenalin cream" and with another cream in conditions associated with deep pain. Ann. Rheumat. Dis., 10:359-364, 1951.

MEDICAL STATISTICS

"Statistics are curious things. They afford one of the few examples in which the use, or abuse, of mathematical methods tends to induce a strong emotional reaction in non-mathematical minds. This is because statisticians apply, to problems in which we are interested, a technique which we do not understand. It is exasperating, when we have studied a problem by methods that we have spent laborious years in mastering, to find our conclusions questioned, and perhaps refuted, by someone who could not have made the observations himself. It requires more equanimity than most of us possess to acknowledge that the fault is in ourselves."—Hill, A. Bradford: Principles of medical statistics. *The Lancet,* London, 1952.

CLINICAL EXPERIENCE WITH DIBISTINE IN ALLERGIC STATES

S. WILLIAM SIMON, M.D., F.A.C.A., and JOHN J. TOOHEY, M.D.
Dayton, Ohio

THIS investigation was undertaken in order to evaluate the effectiveness of two antihistaminic drugs in combination, using one half the average therapeutic dose of each. Dibistine*® is a combination of Antistine® (2(N-benzyl-N-phenylaminomethyl)-imidazoline 50 mg and Pyribenzamine® (N,N-dimethyl-N′-benzyl-N′ (α-pyridyl)-ethylenediamine) 25 mg.

The antihistaminic drugs in general use relieve symptoms in many forms of allergy, especially hay fever, vasomotor rhinitis and urticaria; but they also produce undesirable side effects which in many cases limit their clinical usefulness. The clinical literature lists many reports of the comparative side effects and toxicity of the various antihistaminic drugs, reviewed in detail by Brown.[3] Usually undesirable side effects occur more frequently with Pyribenzamine than with Antistine in therapeutic doses. Loveless and Dworin[5] reported that in eighty-five hay fever patients given Pyribenzamine in 50 mg doses 47 per cent showed side reactions of some degree, while of twenty-five similar cases treated with Antistine in 100 mg doses 24 per cent showed some untoward response. Schwartz and his associates[6] report an incidence of 35.7 per cent undesirable side effects with the former as compared to 22.7 per cent with the later, when using effective therapeutic doses (50 mg of Pyribenzamine and 100 mg of Antistine). Arbesman[1] noted an incidence of 26 per cent undesirable side effects with Pyribenzamine and 14 per cent with Antistine. He also noted that untoward side reactions could be circumvented by decreasing to a smaller but still effective dosage.[2] Dibistine takes advantage of this fact by using one half the usual therapeutic dose of each drug.

In 1950 Hubbard and Berger[4] used a combination of Thephorin® and Trimeton® in the treatment of allergic vasomotor rhinitis in an attempt to counteract the undesirable sedative effect of Trimeton through the stimulatory effect of Thephorin. They concluded that the combination of the two drugs, using full therapeutic doses of each, afforded a greater degree of symptomatic relief than either of the two drugs taken separately. The incidence of all side reactions with the combined drugs was the same as that observed with Thephorin alone, but greater than that observed with

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Doctor Simon is Chief, Allergy Clinic, Brown General Hospital, Veterans' Administration Center, Dayton, Ohio.
Doctor Toohey is Resident in Medicine, Brown General Hospital, Veterans' Administration Center, Dayton, Ohio.
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*Supplied through the courtesy of the Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

Trimeton alone, although the number of severe side reactions observed with the combination was not greater than observed with Trimeton, and significantly less than observed with Thephorin. There was therefore a decrease in the incidence of severe side reactions which they attributed to a definite, though incomplete, antagonism in the side reactions of the two drugs.

PROCEDURE

Most of the patients selected for this study were chronic cases who had been under observation and definitive treatment for some time prior to the therapeutic trial. The average age of the patients was fifty-two years, and the duration of the disease was from one to thirty years. The patients found sensitive to inhalant allergens were receiving standard immunization injections, and where a food sensitivity was demonstrated, they had been placed on an elimination diet. The patients were seen at least once a week and questioned concerning the effectiveness of the drug and untoward side effects. Each patient received Dibistine, one tablet four times daily, when symptoms appeared or just prior to the appearance of symptoms when they were known to occur at approximately the same time each day.

Fifty cases were selected for this study, twenty-four with seasonal allergic rhinitis, fourteen with perennial allergic rhinitis, and twelve with urticaria and angioneurotic edema. In the cases of rhinitis, improvement, in general, meant greatly lessened sneezing and nasal discharge with little effect on nasal blockage. There was lessened pruritus, swelling, and whealing in the cases of urticaria and angioneurotic edema.

RESULTS

	Number of Patients	Improved	Not Improved	Side Reactions
Seasonal Allergic Rhinitis	24	24	0	1
Perennial Allergic Rhinitis	14	12	2	1
Urticaria and Angioneurotic Edema	12	10	2	1
Totals	50	46	4	3

The above table graphically demonstrates the number of patients, the various allergic states treated, and the therapeutic results. The series is too small for arriving at statistically significant percentage figures, but of the fifty cases studied 92 per cent were improved. Undesirable side effects were encountered in only six per cent of our cases and were mild, consisting of slight drowsiness and depression. It was deemed significant that of the various antihistaminic drugs used by these patients, Dibistine gave the fewest untoward reactions and was equally effective from a therapeutic standpoint.

DISCUSSION

We have evidence from this study that a combination of Pyribenzamine and Antistine, each in one half the usual dosage, is effective therapeutically in the treatment of allergic states and is almost totally free of undesirable side effects. It is worthy of note that several patients who experienced

drowsiness after 50 mg of Pyribenzamine alone had no significant complaints after taking two Dibistine tablets containing a total of 50 mg of Pyribenzamine and 100 mg of Antistine. This may possibly be explained on the basis of antagonism in the side reactions of the two drugs; Antistine had previously been reported by Seyler[7] to produce wakefulness rather than sedation, although in general it is considered to be more free from sedative action than Pyribenzamine without producing actual stimulation or insomnia.

Many of the patients in this series had previously taken a variety of antihistaminic drugs over a period of several years. Those who had experienced undesirable side effects from other drugs invariably preferred Dibistine for daytime use. If the sedative action of an antihistaminic drug is desired, naturally others will be more satisfactory.

Dibistine was compared not only with Pyribenzamine alone, but also with an antihistaminic drug of small dosage and few side reactions (Chlor-Trimeton®); the latter drug even in 2 mg doses has produced side reactions in some individuals in whom none occurred after Dibistine. One would expect more side reactions as the dosage of any antihistaminic drug is raised, and this has been our experience. However, with Dibistine the number of patients experiencing side reactions has been less than with other antihistaminic drugs.

SUMMARY AND CONCLUSIONS

A combination of two antihistaminic drugs (Antistine and Pyribenzamine), using one half the average dose of each, has given good therapeutic results with a minimum of undesirable side effects. The excellent results obtained with the combined smaller dosages may be due to potentiation or synergism; however, proof of this would be extremely difficult to establish. The absence of significant side effects may be explained on the basis of smaller dosage of each drug and possibly some antagonism to the side reactions, at least in certain individuals.

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The Editor's Page

ONE TO ONE

Those of us who do not, *in toto*, accept the present-day theories of psychoanalysis as applied to allergic disorders, find ourselves in a particular quandary. If we appear to object to some of the implications of what we read in the literature, it is the allergist who has been analyzed who appears to take the aggressive attitude. Jumping into another frame of reference, he labels us as "hostile" and "resistant." We are told that we do not accept the conclusions of psychoanalysis because they are emotionally repugnant to us. Unfortunately, he goes on to say that few of us are suitable for analysis, and of those few, still fewer either have access, time, or the fees necessary. Under these circumstances, the arguments leave us with both feet planted firmly in mid-air.

Is there any other explanation of our attitude, one which is not a rationalization of our supposed fears and repressions? Some of us, as open minded as the rest, feel that the case is not proven. Perhaps we are wrong to insist on closer correspondence between cause and effect, but the history of medicine as a science demonstrates clearly that those who do insist on a proven one to one correspondence are more often right than wrong, especially in the fields of physiology and immunology.

As we go back into the history of human progress, we find it paralleled by what might be termed the history of human stupidity. Each generation has it own devils, its own exorcisms. The woods beyond the light of our fire is peopled with ghosts, and no matter how bright the fire, the woods extend that much further beyond its beams, and always, the darkness is peopled by ghosts. It appears as though the cause of any phenomenon we do not understand forces us to invent a devil, call him what we will. The inventions of a succession of useful, or good "devils" are among the most productive manifestations of the human mind. The creation of others, however, has retarded human progress.

When the materialists of the Nineteenth Century stated flatly that man had no soul (although they did grudgingly admit that there were many human activities otherwise inexplicable), the road was paved for the Christian Scientists to be equally dogmatic in stating that he had no body. Infectious disease, broken bones, and death itself, notwithstanding, were inexplicable, but nevertheless purely materialistic concepts, worthy only of contempt.

In medicine, the development of physiological chemistry and pathology fixed our attention on first and last causes. The immediacy with which we request laboratory studies for our patients attests to our acceptance of the first. Our death certificates show how firmly we believe in the

second. According to the law, a man, we say, cannot die excepting of something.

The physiological chemist or the pathologist acts as though a man had no soul. Their colleague, the analyst, truly acts as though he had no body. The fact that you can eat a calf's brains, but you cannot eat its mind, seems to escape the extremists of both groups.

A survey of analytical literature shows few instances of the use of those temperate words, "as though." Let us examine some choice tidbits.

A number of nulliparous women are recorded as having adopted children, and thereafter having conceived their own. The analytical literature implies that their neuroses were causing their infertility and that the newly awakened maternal instincts led to the process of conception. What records, if any, have we of women who, after periods of infertility, and without adopting children, become fertile? How many equally infertile women are there who have adopted children and have not become fertile? The one to one correspondence is not only not proven, but men and women everywhere act (and with good reason) as though the exact opposite were true.

Neuroses in young women have not been the cause of infertility sufficiently often for us to advocate their presence as a reliable method of contraception, because in this frame of reference, we have incontrovertible evidence of a very close one to one correspondence mediated quite otherwise, the results of which are very real infants available for adoption.

And, in the same way, if and when we are told that a high percentage of allergic children are maternally rejected, we must again subject the evidence to cool and unprejudiced examination. Are there no ambivalent mothers? Are not all children, expecially those ill with any complaint, often a damned nuisance and, therefore, temporarily the cause of rejection? Is it possible that the child projecting a sense of guilt because he is ill and not knowing why, but thinking it his own fault, acts as though he were rejected? Or is it that a basically immunologically caused illness is only made worse if maternal rejection is present to too great a degree? Our acceptance of the fact that any illness of any type may be exacerbated by more than the usual amount of maternal rejection, universally part of all mothers, can bring our feet back on the ground.

At the heart of the matter, then, it appears that an allergic child suffers exacerbations due to a number of first causes, as exposure to his allergen; second causes, as physiological states; and third causes, as psychological responses, among which maternal rejection may be one. Eliminate, let us say, an animal dander, and the other causes operate rarely, if at all.

When we see a child exposed to a nasal test with ragweed, with immediate response, we are certain of cause and effect. When we are told that he wheezed because on Tuesday night his mother rejected him, we are not so certain. The better our allergy, the less need for other forms of treatment. One does not use a steam roller to crush a gnat.

The psychosomaticist can say that any one type of illness is associated with a fairly clear-cut personality pattern. Those who are accident-prone, or hypertensive, or of the peptic ulcer type, act as though such general patterns were present. A number, however, do not.

The supposition that stress, like the hypothetical occupant of a nearby woodpile, is the answer, is not sufficient. The nonacceptance of a supposition which appears as though it were only occasionally true, should not lead to name calling. The papers have been published and are available to all those who wish to read them. The philosophical concepts are magnificent. The relationship to the actual cause of many illnesses, however, is not proven.

A review of ten years of analytical literature dealing with the results of its therapeutics reminds one of the old Jesuit who was asked to present the evidence for immortality. It took him all of five minutes, following which he said, "That is all the evidence there is."

Smiling wistfullly, one of his listeners said, "If that's all there is, one wishes there were more."

THE TEXAS POLIO TESTS*

The whirling, topsy-turvy pattern of medical progress with its day-by-day and week-by-week advances and retreats often is confusing to the public and indeed to the profession itself. The most recent illustration is the experiment now under way in Texas by the National Foundation for Infantile Paralysis to test the value of gamma globulin as a preventive measure in poliomyelitis. Some 35,000 individuals will receive injections—half with gamma globulin and half with gelatine as mere control.

One may wish the experiment every success. The irony is that only a year ago, in the summer of 1951, the National Foundation and many public health officers were warning the public and the profession alike against the possibility that the severity of paralysis, in polio cases, appeared to be slightly greater for patients with a prior history of injections than in cases which had not received injections.

Much confusion and alarm resulted in the public mind. Some people jumped to the conclusion that no injections ought to be given during the season of polio. After several further clarifications on the wording of the health department rulings, it finally came out that a doctor could, with safety, give all injections necessary in treating almost any disease but that optional injections might well be delayed until the fall season.

A year later, in this summer of 1952, mass injections of a prophylactic nature and certainly optional, are being given by the tens of thousands by the Polio Foundation itself.

The use of gamma globulin to help prevent the onset of polio recalls that in the 1930's there were high hopes convalescent serum from polio patients might, in turn, have prophylactic value in warding off the disease. Aycock and Park in the early 30's reported favorable results. Later Aycock reversed himself. By 1939 Levinson was reporting good results (a reduction by a factor of ten in paralysis) by massive doses of convalescent serum up to 200 cc. and 300 cc. Other workers were less enthusiastic and the whole method was generally abandoned because of the inconclusive results. One possible explanation for Levinson's findings was that he administered far higher doses of serum than those who failed to achieve his results. . . .

If the Texas research proves valuable, if the use of gamma globulin does show a reliable and statistically sound decrease in the onset in polio, then Levinson and the other pioneers who advocated the use of convalescent serum will indeed be vindicated. The wheel, indeed, will have turned a full cycle.

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*Courtesy of the author, Robert D. Potter, Executive Secretary, New York County Medical Society and *New York Medicine*.

The Fiftieth Anniversary of the Discovery of Anaphylaxis

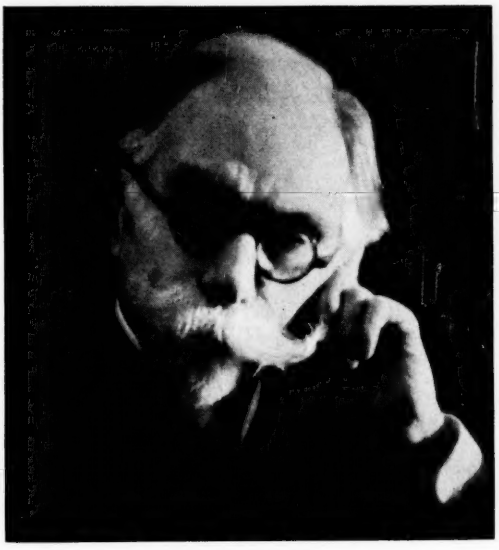
The evening of May 13, 1952, marked the fiftieth anniversary of the discovery of anaphylaxis* by a group of scientists and their colleagues, at the Richelieu Theatre in the Sorbonne, Paris. The Comité d'Honneur consisted of:

S. A. S. Prince of Monaco, President
Ch. Best (Nobel Prize)—Canada
L. Binet, Dean of the Faculty of Medicine of Paris
J. Bordet (Nobel Prize)—Belgium
Sir H. H. Dale (Nobel Prize)—Great Britain
D. Danielo-Polu—Roumania
C. Frugoni—Italy
C. Heymans (Nobel Prize)—Belgium
B. A. Houssay (Nobel Prize)—Argentina
A. Lemierre, President of the National Academy of Medicine, France
T. Madsen—Denmark
P. Portier, The Institute—France
F. M. Rackemann—U.S.A.
A. R. Rich—U.S.A.
B. Schick—U.S.A.
F. Wittich, President, International Association of Allergology—U.S.A.
Ch. Richet, Secretary-General—France
B. N. Halpern, Secretaire-Adjoint—France

It was most fitting that this epochal discovery in the history of medicine should be suitably and proudly honored by the French scientists. The days preceding and following the meeting were marked by receptions for the Comité, luncheons, and dinners. On May 11 there was a luncheon at the residence of Prof. Charles Richet, son of the elder Richet. On Saturday morning, May 13, André Marie, Minister of National Education, introduced from the estrade at the Pont-Royal Hotel Professors Portier, Richet, Vallery-Radot, and Madsen, and Doctors Halpern and Wittich. That afternoon there was a luncheon at the residence of Prof. Pasteur Vallery-Radot. That same afternoon a reception was held at 5:00 p.m. in the l'Ecole de Medecine, and at 7:00 p.m. a dinner was given by Dr. Bernard Halpern preceding the meeting at 9:00 p.m. at the Sorbonne. The Prince of Monaco was unable to attend and sent his deepest regrets. Prof. Léon Binet, Dean of the Faculty of Medicine, introduced all the speakers and mentioned the writer as a representative and an officer from the United

*P. Portier and Ch. Richet: De l'action anaphylactique de certains venins. Compt. rend. Soc. de biol., 54:170, 1902, and Travaux du lab. de physiol., 5:506, 1902.

States. Prof. Pasteur Vallery-Radot of the Academy of Medicine made an introductory address about the anniversary. Prof. Paul Portier, member of l'Institut and Director of the Oceanographique Institut of France, spoke on "The Birth of Anaphylaxis." This was followed by the reading



PROFESSOR PAUL PORTIER
Member of l'Institut and
Director of the Oceanographique Institute of France.

of Sir Henry Dale's (Nobel Prize) paper on "The Mechanism of Anaphylaxis," read by Dr. B. Halpern in the absence of Sir Henry because of illness. Prof. Léon Binet of l'Institut and Dean of the Faculty of Medicine, presented the biography of Charles Richet, the discoverer of anaphylaxis. His son, Prof. Charles Richet of the Academy of Medicine, then presented a paper on "Alimentary Anaphylaxis."

The proceedings of the Anniversary Program appear in *La Presse Medicale* for May 10, 1952, volume 60, number 32.

Charles Richet was born in Paris, August 26, 1850, the son of Alfred Richet, professor of surgery of the renowned Medical Faculty at the University of Paris, and a member of the Institute of France. Richet was educated in Paris and in 1869 began the study of medicine. While at the University he was an assistant to the surgeons LeFort and Verneuil. With an increased appreciation of physiology he studied under the most outstanding physiologists of his time: Marey, Berthelot, and Vulpian. He received his medical degree in 1877 and his Ph.D. in 1878, and in the same year he was appointed as "agrégé." In 1877 he was appointed professor of

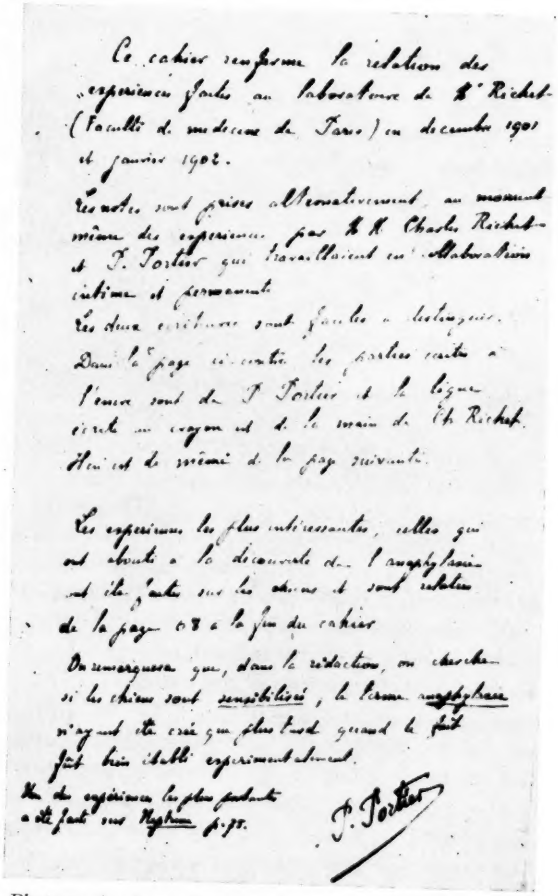
physiology at the Medical Faculty in Paris, which chair he held for forty years.

Besides his medical accomplishments he was a philosopher and a man of

Photograph of notations in the diary of experiments on the dog Neptune by Ch. Richet and P. Portier, the original work on the phenomenon of anaphylaxis. (Courtesy of P. Portier)

literature. He wrote dramas of recognition as well as novels and poetry. As a philosopher he wrote his "Selection Humaine." His versatile interests are too numerous to mention here. He considered as indispensable the union of physiology and medicine, which is to say, the science of life and the science of healing sickness. His great aim was to coordinate the laboratory of the Faculty of Medicine with the doctors. His studies with many collaborators on lactic acid fermentation led him to defend the

theory of heredity of some acquired characteristics. His studies on gastric secretion are noteworthy as well as those of heat regulation. His most important researches concerned immunologic phenomena, the physiology



Ce cahier renferme la relation des expériences faites au laboratoire de M. Richet (Faculté de médecine de Paris) en décembre 1901 et janvier 1902.

Les notes sont prises alternativement au moment même des expériences par M.M. Charles Richet et P. Portier qui travaillaient en collaboration intime et permanente.

Les deux écritures sont faciles à distinguer.

Dans la page ci-contre les parties notées à l'encre sont de P. Portier et la légende écrite au crayon est de la main de Ch. Richet. Il en est de même de la page suivante.

Les expériences les plus intéressantes, celles qui ont abouti à la découverte de l'anaphylaxie ont été faites sur le chien et sont relatées de la page 108 à la fin du cahier.

On remarquera que, dans la rédaction, on cherche si les chiens sont sensibilisés, le terme anaphylaxie n'ayant été créé que plus tard quand le fait fut bien établi expérimentalement.

Une des expériences les plus probantes a été faite sur Neptune p. 97.

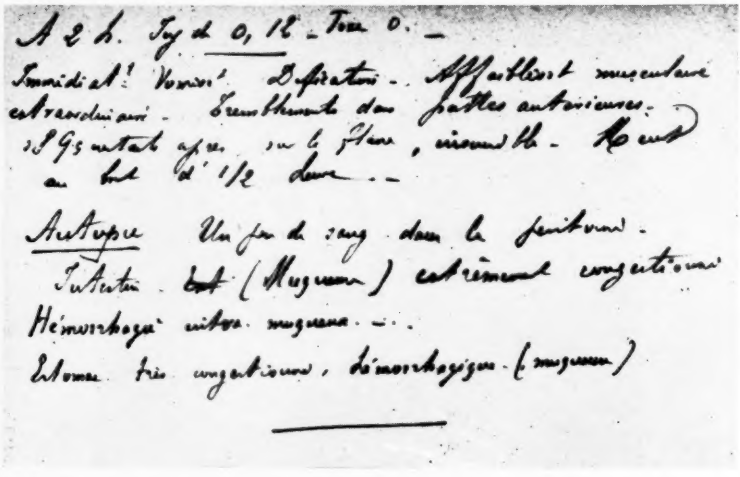
P. Portier

Photograph of notations in the diary of experiments on the dog Neptune by Ch. Richet and P. Portier, the original work on the phenomenon of anaphylaxis.

of nerves and muscular systems, of the liver and the respiratory system, and the mechanism of heat regulation.

The later years of Richet's life were devoted mostly to psychological research. Among his many publications there are six large volumes of "Travaux du laboratoire de physiologie de la Faculté de Médecine de Paris," while his "Dictionnaire de physiologie" is published in eleven volumes, not to mention his monographs on "La chaleur animale," "Leçons

sur les muscles et les nerfs," "Essai de psychologie générale," "Traité de metaphysique," and, finally, his wonderful monograph on "L'anaphylaxie," first published in 1912.



Photograph of notations in the diary of experiments on the dog Neptune by Ch. Richet and P. Portier, the original work on the phenomenon of anaphylaxis.

At the age of eighty-five years Richet died in 1935 at the end of a most productive life. All human activities aroused his interest, he worked prodigiously for humanity and progress, and all the time he was learning and teaching. He was truly a teacher of the world.

To Richet and his associates (1898-1902) must go full credit for the discovery of anaphylaxis, which is the basic phenomenon of allergy. It was very fortunate that he lived long enough to see his concept fully developed. Their initial experiments were performed on the yacht of the Prince of Monaco in the Indian Ocean on July 5, 1901. The yacht, *Princesse Alice II,* left from Toulon. The prince directed the operations, and Drs. Jules Richard and Neveu Lemaire were also in the party. Richet and Portier undertook a study of the toxic, or urticarial, substance of a variety of jellyfish known as the "Portuguese Man-of-War." Since these investigations were incomplete, upon their return to Marseilles September 19, they continued their studies in the physiology laboratory of the Faculté de Médecine in Paris. There they worked with the sea anemone, a variety of stinging nettle. Richet, believing that the urticating principle is a toxin, injected an extraction of the sea anemone into dogs. To his astonishment he noted that the same extract which had proved harmless on the first injection sometimes would produce severe toxic symptoms, or even death, of the animal on reinjection after several days. Although this altered reaction

had been previously noted by other observers, it merely aroused curiosity; and it remained for Richet and his associates, Harricourt and Portier, to explain and work out the mechanism of anaphylaxis. In 1902 they therefore proposed two basic concepts, both of which remain confirmed today: (1) a foreign substance which, on first injection, may be relatively harmless, may, on reinjection, become severely toxic, even fatal, when given in the same or even smaller dosage; (2) an interval of several days must elapse between the first and second injections (Vaughan and Black: *Practice of Allergy,* p. 12). They believed that during the intervals of these injections some profound change took place which altered the tissues so that some natural protective mechanism was destroyed or removed which rendered the animal susceptible to the toxic action of the original substance. At first they believed that there was a primarily toxic action in this urticarial substance against which the body protected itself. At this time interest in the phenomenon of immunity was at a high peak, and Richet and his co-workers really thought in terms of immunity. Richet's concept of the removal of this natural immunity factor during a ten-day incubation period justified his selection of the term *anaphylaxis* (lifting up or removal of protection). This term contrasted with *prophylaxis* (favoring protection), a term employed at this time in discussions of immunology.

Although Richet at the outset believed that this anaphylactogenic substance must be primarily toxic, his postulates also held with nontoxic substances, which justifies his being called "the founder of experimental anaphylaxis." In 1913 Richet was awarded the Nobel Prize in Physiology and Medicine by the Caroline Institute in Stockholm for his work on anaphylaxis. In his Nobel Prize lecture he summarized his own basic contributions to the field of allergy and outlined the main roads for future research, and it is as stimulating at the present time as it was then.

During the first World War Marshal Foch conferred upon Richet the Grand Croix de la Legion d'Honneur for his valuable performances with the Sixth Army in the winter of 1918.

It was the writer's good fortune to see the original pencilled notes of Richet and Portier written on the yacht *Princesse Alice* comprising the work done on the dog named Neptune. For those interested these notes are published for the first time.

Few scientists have reached the pinnacle of success attained by Richet through devotion to medical science for the benefit of humanity. His work, along with that of Pasteur and other notable French scientists, will make France a shrine for scientists for all time.

—Fred W. Wittich, M.D.

Progress in Allergy

ACTH AND ALLERGY

ETHAN ALLAN BROWN, M.D., F.A.C.A.
Boston, Massachusetts

(Continued from the May-June issue.)

ACTH AND THE TISSUES

At the moment (March, 1952) there is some controversy as to the exact name of the hormone which is the subject of this discussion. There are those who argue for *adrenocorticotropin,* a term rapidly becoming acceptable, if only by its widespread use, as against *adrenocorticotrophin* which probably more clearly defines its function. Since such functions are in the process of investigation, the following discussion is limited to a brief summary of the accepted, although superficial, physiological principles involved and their ramifications, as seen in clinical studies in normal, otherwise, healthy, and abnormal, otherwise sick, patients. It has been difficult to separate physiological effects from side reactions, since either is a subjective judgment depending entirely upon the point of view of the investigator. This and the following sections which are devoted to immunological and to side reactions, therefore, necessarily overlap.

We know that ACTH is derived from the acidophil cells of the anterior pituitary gland. Such release may depend upon activation of the gland by the sympathetic nervous system or else again by a decrease in the blood levels of ACTH. For the first type of stimulation, probably associated with stress, epinephrine as derived from the adrenals is probably part of the mediating mechanism. The second type of activation probably depends upon metabolic requirements.

We know that ACTH causes an increase in the secretion of adrenal steroids and that these can be grouped into three classes: the glucorticoids, the mineraloglucocorticoids, and the third group known as "N" hormones responsible for anabolic and androgenic activity.

The steroids are both structurally and functionally related. Metabolically, they are known to increase the conversion of proteins to carbohydrate and of carbohydrate to nitrogen causing a rise in the blood sugar level. They mobilize and utilize fats and, as a result of increased protein catabolism or decreased protein anabolism, cause a negative nitrogen balance. They increase the antihyaluronidase activity of the body, increasing its resistance to certain forms of stress. They may cause moderate sodium and some water retention. Their presence in excess depresses the number of circulating lymphocytes and eosinophil cells and affects the lymph nodes. High levels in the blood stream act upon the adrenal cortex and the thymus, depressing the functions of both.

The adrenal steroids associated with mineral balance cause urinary retention of sodium and chloride, with a decreased concentration of both in perspiration, associated with an increased plasma and extracellular fluid volume. They cause urinary excretion of potassium directly or due to protein catabolism. Some of the potassium excreted is said to be caused by its replacement in cells by sodium.

The "N" hormones play a part in the development of the secondary sex characteristics and also are related to mineral balance, although they, in their turn, cause retention not only of sodium chloride but also of potassium, phosphorus, and nitrogen.

The injection of ACTH into the body causes a depression of the anterior pituitary and excitation of the adrenal glands. Their state at the time of stimulation, the amount of such stimulation, and the general state of the body at the time are all involved in the widespread effects which are only now beginning to be recognized. From the more than two thousand papers available on this aspect of the subject, the following have been chosen as being particularly interesting to allergists because they illuminate some little known aspect of the subject, or else again, because they help achieve some clarity in an otherwise confused physiological picture.

The routine therapeutic response to ACTH is reduction of fever, disappearance of pain, increase in appetite and sense of well being, inhibition of inflammation and swelling, reduction of the eosinophil count, return to normal values of the sedimentation rate, and correction of co-existing secondary anemia. The return of fever is said to prove that the dose is too small or that a concomitant infection has recurred. A return of pain, especially if abdominal, suggests untoward side reaction.

Although the effects of overdosage are reversible, those ordinarily seen include edema formation controllable by low sodium chloride, high potassium chloride intake; hypertension; signs of potassium deficiency, as muscle weakness, fatigue, or paresthesias; glycosuria, hyperglycemia; psychotic changes; negative nitrogen balance, as shown by loss of weight; and miscellaneous side reactions as mooning, hirsutism, acne, and cutaneous striae.

The relative contraindications are said to be hypertension, diabetes, congestive heart failure, peptic ulcer, tuberculosis, active infections, and certain psychoses.

The absolute contraindications include again active or recently healed tuberculosis, active or recently healed peptic ulcer, hirsutism, Cushing's syndrome, chronic glomerulonephritis, and known psychoses.

In studying the effects of ACTH in patients with mental disease, Altschule et al found the change in the eosinophil count, uric acid, and 17-keterosteroid excretion and sweat sodium to be no different in psychotic as compared with nonpsychotic subjects, but that the patients with schizophrenia or manic-depressive psychoses showed greater than normal changes in carbohydrate metabolism after the injection of ACTH.

Archer[117] draws our attention to the fact that few or no references have been made to the relationship of ACTH to lipid metabolism and fatty infiltration of the liver. Since fatty infiltration of the liver is a common autopsy sign in Cushing's syndrome, it seems plausible that the injection of ACTH may be followed by rapid mobilization of liver fat. This may be sufficient to promote a mild hepatic dysfunction responsible in part for some of the biochemical changes produced by ACTH, especially the diminished sugar tolerance and the tendency to glycosuria, the occasional increased plasma cholesterol and the rare ketosis. These same changes are seen in the two conditions which benefit rheumatoid arthritis, namely, pregnancy and jaundice.

In a masterful paper on the histology of the lymphoid glands of rats treated with ACTH, Baker, Ingle, and Hao Li[118] discuss the problems involved in discovering the action of adrenocortical steroids on lymphoid

tissues. They draw attention to the fact that it is not clear whether the lymphopenia, seen also in humans, is due to accelerated lymphocytolysis, retarded proliferation of the progenitors of lymphocytes, or to a combination of both factors. This information is important because of the hypothesis that under the action of adrenal steroids, the lymphocytes undergo lysis, liberate antibodies, and increase the level of serum protein. In man, the partition of proteins as determined by electrophoresis and the level of antibodies in the serum remain unchanged after treatment with adrenocorticotropin. They conclude from their work that it seems clear that the adrenal steroids secreted under the influence of ACTH have a direct effect on the lymphoid organs, but determination of the relative significance of their indirect or supportive role under stress require additional investigation. The animal studies show, as a result of ACTH injections for a period of up to twenty-one days, that lymphocytes and thymocytes are not produced. Changes seen in the thymus are similar to those reported to be elicited by stress. These studies may point a way to clearing the controversy as to the anatomical effects elicited in the lymphoid organs of humans by ACTH injections.

Bonner and his colleagues[119] have shown that in aged, debilitated patients, ACTH causes a decrease in circulating eosinophils similar to that observed in healthy subjects. Twelve of fourteen cancer patients responded normally, and six of twelve without cancer showed normal, and the other six a subnormal, eosinopenia. The uric acid-creatinine ratio increased 100 per cent more in three patients with and in three without cancer. It is suggested that the modified response in these patients was due to age and not to disease. In two diabetic patients with cancer, the fasting blood sugar level increased 75 and 148 per cent respectively, after an injection of 25 mg ACTH. The increase in two diabetic patients without cancer was 27 and 33 per cent respectively, that is, less than the maximal response seen in nondiabetic individuals.

In a later communication, Bonner[120] discusses the factors that affect the value of eosinophil counts and eosinophil levels when these are taken as an index of adrenal responsiveness. Allowing for the known variables, he suggests that four chambers or 800 cells be counted and that in the laboratory where many eosinophil counts are done by the same personnel, the chamber method be used. Because it has been shown that fasting alone will cause an eosinopenia, and because it has also been demonstrated even in nonfasting subjects that there is a consistent eosinopenia in the forenoon with a rise later in the afternoon, the tests should be done on a nonfasting patient between 1:00 and 5:00 p.m. Interestingly enough, he suggests that other mechanisms exist for the control of eosinophil levels, and that these may account in part for the fact that the same subject will respond differently to the same stimulating dose of ACTH at different times. Brown[121] had discovered some of these factors to be true in his mathematical analysis of the Leucopenic Index.

Caramanian[122] demonstrated that in eight patients treated with cortisone there was generally a decrease in circulating eosinophil cells after an intramuscular test dose of 25 mg ACTH on the first day of therapy. Toward the end of prolonged treatment periods, however, the test became strongly negative (an increase in circulating eosinophil cells after a test dose of ACTH) indicating, therefore, adrenal inertia. The tests remained negative for ten to thirty days. In patients treated with ACTH alone, the test took an average of twenty-five days to reverse itself.

Castor and his colleagues,[123] measuring the evidence that indicates that

ACTH hormones exert important effects on the central nervous system, studied such effects on the anatomy of the brain. In man, euphoria, psychotic reactions, restlessness, convulsions, and electroencephalographic irregularities have been observed. These psychotic states have been correlated, also, with decreased adrenal rsponsivity to ACTH. Although it has been suggested that the hypothalamus controls the secretion of ACTH by the anterior hypophysis, there is no agreement concerning the localization of this function in the hypothalamus. Since it has previously been discovered that lesions in the posterior region of the tuber cinereum and in the mammillary body abolished the lymphopenic response to stress in rabbits and stimulation of these regions result in a lymphopenia, it is concluded that secretion of ACTH may be under neural control via the hypothalamus and the hypophyseal portal vessels. Using rats as experimental animals, it was discovered that treatment with ACTH caused consistent cytological changes only in the hypothalamic paraventricular nucleus. The authors agree with other workers in this field that the paraventricular nucleus exerts its control over the hypophysis by humoral rather than by nervous means. Their conclusion correlates well with the cytological changes described in their present work. Because the hypothalamus is known to play an important role in the regulation in emotional expression, their observations, therefore, may be of some assistance in understanding the changes in personality which sometimes are observed clinically following treatment with ACTH.

Cleghorn and Graham[124] used as a cumulative index of adrenocortical activity comprising the sum of arbitrary figures denoting the degree of change in circulating neutrophil, lymphocyte, and eosinophil counts and in the ratio of urinary uric acid/creatinine. This index was higher on the average for thirty psychoneurotic patients than for three schizophrenic patients receiving ACTH in doses of 2.5-25 mg. Of twenty-two subjects receiving saline injections, those demonstrating a greater degree of anxiety had higher indexes, and vice versa. Electroconvulsive therapy in nine patients produced adrenocortical activity comparable to that produced by approximately 5 mg ACTH in another group of patients. Previous sedation with Sodium Amytal decreased such activity.

The usefulness of the lymphopenic response as an index of ACTH secretion was demonstrated by a series of ingenious experiments by Golfer and his colleagues.[125] Subcutaneous Faradic stimulation over the lumbar vertebrae, or restraining clamps for one to two hours served as a stress stimulus in normal rabbits almost always causing a lymphopenia within three hours. This was usually accompanied by a granulocytosis. Hypophysectomy led to an abolition of the lymphopenic response to stress in all animals when tested within two weeks of operation. During this time, however, the injection of ACTH caused the usual reduction in the lymphocyte count. Of eight animals so tested, four showed no response. In the four in whom some response was obtained, post-mortem examination proved the hypophysectomy to have been incomplete. The intravenous injection of epinephrine 1:150,000/1 ml gave rise to lymphopenic response in one case. The authors conclude that a reduction in the lymphocyte count can be used as an index of anterior pituitary secretion in experimental work, provided that the subject is not exposed to incidental emotional stress.

One of the most important papers in this field by Cosgriff et al[126] described eleven thromboembolic episodes, two of them fatal, occurring among 175 patients receiving ACTH or cortisone for varying lengths of time. The venous clotting time was considerably shortened in five of

such patients. Heparin-retarded venous clotting time was considerably decreased in four of five patients receiving ACTH. The mechanism in the change of blood coagulation is not clear, since the patients presented normal protamine titration and heparin tolerance tests. Using three normal subjects as controls, a single injection of 20 mg of ACTH was followed in four hours by a prolongation in the clotting time accompanied by an increase in heparin or heparin-like material. There were no consistent changes from patient to patient. Despite the tentative nature of the data so far obtained, there appears to be little doubt that the adrenal cortex is involved in several aspects of the coagulation process.

The effect of ACTH and cortisone on phagocytosis was studied by Crepea and his colleagues,[127] who showed that nine of ten patients treated with ACTH showed a decrease in the phagocytic activity of the neutrophilic leukocytes, an increase occurring in the one patient due, however, to the development of specific antibodies during the treatment period.

Although we are warned not to use ACTH in patients with diabetes, it is occasionally necessary when a second disorder requiring hormone treatment is present. Fajans and his co-workers[128] gave a patient with diabetes mellitus and subacute myelogenous leukemia, a total of 2,875 mg of ACTH in twenty-two days. A glycosuria which at times exceeded all available dietary carbohydrate, a tremendous negative nitrogen balance, insulin resistance, and an increase of the leukemia were observed. On the other hand, ketonemia and ketonuria were minimal or absent in the presence of essentially total diabetes and insulin resistance. The authors conclude that the ACTH appears either to accelerate the process of ketolysis in the body or to decrease hepatic ketogenesis.

Fortier, working with Selye and his group,[129] did a comparative study of some of the chemical and morphological changes elicited in the adrenals both by stress and by purified ACTH. The stress consisted of cold, fasting, and spinal-cord resection with which the effects of single and repeated injections of ACTH were investigated and compared. A single injection of ACTH produced a rapid but very transient fall of adrenal stainable lipids. No such decrease was observed after twenty-four to forty-eight hours of repeated injections despite the marked depletion of the cholesterol and ascorbic acid content. This is in distinct contrast to the pictures observed after systemic stress of the same duration following which all the above adrenal constituents are proportionately decreased. The authors conclude that ACTH alone cannot account for the adrenal response seen during the alarm reaction.

To round out the picture, Gemzell et al[130] demonstrate that there is an increase in ACTH after adrenalectomy. Starting with a method for estimating plasma ACTH after adrenalectomy, they can calculate its rate of formation and secretion by the pituitary. The studies revealed that the adrenal gland itself, through formation of cortical steroids, controls the secretion of corticotropin by the pituitary. Removal of the adrenals is reflected in an immediate and progressive increase in ACTH secretion. This causes the pituitary ACTH content to decrease until the progressively increasing ACTH formation by the pituitary causes it to rise again. Adrenalectomy does not appreciably affect the disappearance rate of ACTH. Three weeks after adrenalectomy a new approximately steady state is reached, characterized by a corticotropin content in the pituitary one and a half times normal, an increased ACTH content in the body fluids at least thirty times normal, and an increased corticotropin formation and secretion rate also at least thirty times normal.

According to Gordon,[131] prolonged therapy with ACTH may result in steadily decreasing effectiveness. In rats, repeated injections of ACTH cause a diminishing reaction to test doses, although a control group showed a consistent depletion of adrenal ascorbic acid after similar doses. The author concludes that the sera from the treated animals apparently contains a substance which also inhibits the adrenal ascorbic acid depletion in hypophysectomized rats given a test dose of ACTH. The dosage level which produces a refractory state in rats is similar to that used in the treatment of rheumatoid arthritis in human beings. Although the serum from ACTH-treated animals consistently decreased the response to a test dose of ACTH, activity of the antiserum was not demonstrable *in vitro* by a precipitin technique.

The similarity of the effects of ACTH and various types of shock therapy is demonstrated by the paper published by Henneman and Altschule.[132] The concentration of reduced glutathione in the erythrocytes was determined in psychotic and severely neurotic patients before and after electric convulsion therapy, ambulatory insulin therapy, intramuscular epinephrine (0.1 ml/kg) and 25 mg of ACTH. The blood glutathione level was increased by 20 to 150 per cent in twenty patients, two to four hours after electric shock treatment with a similar rise of 16 to 54 per cent occurring after epinephrine injections in fifteen patients. A smaller and less consistent increase of the same type was seen after ambulatory insulin treatment and injections of ACTH.

One of the best papers on the subject is Ingle's[133] on the functional interrelationships of the anterior pituitary and adrenal cortex. Presenting the hypothesis that for many metabloic adjustments the anterior petuitary-adrenal cortex response has a supporting role rather than obligatory regulatory action, he points out that although the primary cause of the diabetic state induced by pancreatectomy is insulin deficiency, yet the disorder is ameliorated by the removal of the adrenal cortices. Similarly, experimental hypertension can be caused by renal ischemia. The exciting cause lies in the kidney, but the blood pressure falls to normal or below when the adrenal cortices are removed. The experimental stresses which cause "adaptation diseases" in laboratory animals fail to do so in the adrenal insufficient animal. The analogy he uses to clarify his meaning is worth quoting in full. He says, "Consider an automobile (organism) whose speed (primary cortical hormone action) is kept constant by a mechanical governor (anterior pituitary). When the load (stress) is increased, the fuel supply (cortical hormones) must undergo an increase in order to keep the speed constant. Under usual conditions, the response of the governor serves to maintain normality under load. A weakened mechanism (unilateral nephrectomy) meeting additional obstacles (high sodium, high protein diet) is much more likely to wreck it ("adaptation diseases") if it sustains a constant speed than is a similar automobile which is caused to run slowly or stall by restriction of its fuel supply. Nothing is assumed to be wrong with the operation of the governor, but it plays an essential, though not the primary, causative role in the resulting damage." He presents evidence to support the hypothesis that the response of the anterior pituitary-adrenal cortex axis during stress plays a homeostatic role and does not represent the exciting cause for many of the metabolic responses to stress.

In another communication, Ingle and his colleagues[134] discuss the effects upon the tissues by continuous injections of ACTH. Twenty-seven normal male rats were force-fed a high fat, low carbohydrate diet. Seven-

teen of these were given continuous subcutaneous injections of ACTH until the animal died or lasted for twenty-one days. Only seven survived. All exhibited glycosuria and acetonuria, temporary in some and sustained in others. Three developed infections. Eleven showed gross pathological changes in the kidneys, and three gross lesions in the heart. Twelve presented ulcers in the pyloric portion of the stomach. Ten normal rats used as controls all survived with no changes of any type.

There is more to the eosinophil response than choosing the correct stain, the technique, and the time of day. According to Kellgren and Janus,[135] who administered ACTH and cortisone to normal subjects, eosinopenia was most pronounced four hours after the injection. They discovered that to produce a fall in the eosinophil count of more than 75 per cent at either four or six hours following injection, doses of at least 20 mg of ACTH were necessary. For oral cortisone, the dose was 50 mg. The degree of response is about equivalent to that obtained following each injection of 10 ml of T.A.B. vaccine.

Reaction of ACTH on thrombocytes has been studied by Koller and Zollikofer,[136] who discovered that intramuscular injections raised the thrombocyte level markedly above the usual peak in its daily fluctuations. A single dose of ACTH 25 mg caused a maximum rise at six hours, which is two hours after the lowest value for eosinophil cells. The thrombocytosis subsides the same day, but the leukocytosis and the low eosinophil and lymphocyte levels may persist for as long as two days.

Corroboration of the effects of ACTH on the coagulability of the blood comes from Monto et al,[137] who showed that an injection of ACTH 20 mg into three normal subjects caused an increase in circulating heparin or heparin-like substances as determined by protamine titration and parallel prolongation of clotting time. In one subject, the coagulation time was reduced by fifteen minutes in less than twenty-four hours. Initial and transient increase in protamine titer and clotting times were frequently encountered, as seen in twelve of twenty patients in whom it decreased after the first twenty-four hours of treatment. The plasma accelerator globulin level, two-stage prothrombin time, and antifibrinolysin were all altered, although no significant changes were seen in platelet counts.

Because of the interrelationship between ACTH and Vitamin C levels of the adrenals, it is of interest to note the work done on the effects of ACTH in experimental scurvy. Nigeon-Dureuil et al[138] gave ACTH in 2 mg doses three times a week to guinea pigs on a Vitamin C deficient diet. At the end of the twenty-sixth day of the experimental period, the weight of the adrenals in the ACTH-treated animals and in the controls were respectively 212 and 136 per cent above normal. Microscopic analysis showed that Vitamin C deficiency produced adrenal insufficiency in the guinea pig and that such effects could not be attributed to pituitary insufficiency.

Morphologic changes in the human adrenal cortex after the administration of ACTH have been made by O'Donnell and his colleagues,[139] as observed in fourteen patients who had received ACTH or cortisone before death. In those who had been given ACTH, there occurred loss of lipids, hypertrophy of the zona fasciculata and zona reticularis, and, in some cases, cortical hyperplasia. The zona glomerulosa appeared narrowed and ill defined and some of the cells hypertrophic, probably due to rapid transformation of its cells to the fascicular type as a means of augmenting the secretory complex. The morphological pattern is said to resemble that seen in stress. The changes following cortisone are said to resemble those

seen in patients in whom there has been destruction of the pituitary. The authors conclude that administration of cortisone induces adrenal atrophy by suppressing the secretion of ACTH.

In reply to a letter by Archer,[117] Pelner[140] agrees and states that he and his colleagues have considered this problem for some time, having advanced the concept that ACTH acts by "occupying" or "engaging" one or more of the liver functions as borne out by the facts that rheumatoid arthritis is improved during pregnancy and episodes of hepatitis, and that the excretion of histidine is increased about 100 per cent after remission due to ACTH treatment, as it is during pregnancy. Other of the phenomena associated with Cushing's syndrome and ACTH treatment are so characteristic of hepatic insufficiency that the word "hyperhepatism" has been coined as characterizing these conditions. Pelner and his associates are engaged in searching for drugs which will "occupy" one or the other of the many liver functions without causing the side reactions of ACTH or cortisone.

For an excellent discussion of the effects of ACTH on connective tissue, the paper by Ragan and his colleagues[141] should be studied. Normal rabbits were pretreated with cortisone for three days before skin defects were made in their ears. They were sacrificed five and nine days after the wounds were made. In the control animals typical granulation tissue appeared, whereas in those treated there was no granulation tissue, the blood vessels lying exposed and visible excepting for a layer of fibrin. With smaller doses of the hormones granulations began to appear by the eighth day, so that the lower dose causes a delay rather than a complete suppression of growth. The authors suggest from their work that in diseases involving mesenchymal tissue such tissues are traumatized by an unknown agent. When hyperadrenalism is induced, the mesenchymal tissues are unable to respond to trauma, and a remission of symptoms resulting from the response of these particular tissues to such trauma follows. They feel that adrenal functions in the diseases which respond to ACTH is apparently within normal limits, and a hyperadrenal state is a condition that effects the remission. It would appear then that trauma such as due to mechanical, infectious, metabolic, or antigen-antibody combinations affect the connective tissue, the changes being blocked by hyperadrenal states. When such blockage does not exist, the connective tissue reacts as shown in alterations of wound healing, in disease activity, or in hypersensitivity.

Although Reiss[142] is chiefly interested in endocrine research and psychiatry, a number of his concepts are applicable to our own subject. He feels that in any patient with a given psychosis, the neuro-endocrine relationship is constantly changing. Although the chief disturbances may be in either the endocrine system or the brain functions yet each of these can cause secondary disturbances in the other, and this in turn is reflected back upon both endocrine and cerebral behavior in a complex vicious circle. He feels that newer methods of treatment including ACTH may make possible a better prediction of success as well as a more logical approach for treatment. In general, ACTH is now being administered without much laboratory control, and such control is actually advertised as not necessary. Reiss states that the dose given to each patient should depend on daily estimations of 17-ketosteroids. Some patients who lack ACTH will respond to as little as 2 mg doses. In others a higher threshold dose may be required. Once the minimum dose is discovered, it should not be increased, since too much ACTH can overstrain and exhaust the

adrenal cortex, reversing the beneficial effects of continued treatment. In patients who give a negative four-hour response even high doses of ACTH may fail to effect the ketosteroid excretion, and no psychological changes occur. In patients with acute catatonia, improvement will last about two days, following which the patient fails to respond to treatment. For emaciated, older depressive patients whose adrenal cortex is underfunctional, small doses (2 mg daily) of ACTH have been effective in raising relatively very low 17-ketosteroid and cortin excretion and improving the psychological state.

Because of the present overemphasis of psychological factors in the management of allergic diseases, it is interesting to note the organic basis of such changes as noted in ACTH therapy. Rome and Braceland[143] studied the mental changes in twenty-six patients receiving ACTH. The variety and degree of such alterations depend upon a number of personality factors, including the meaning of the patient's disease to him and the significance of his improvement. In general, the relief in the largest group of patients can be noted as associated with a feeling of well being, self confidence, an optimistic, elated mood, and an acceleration in the tempo of thinking and physical activity. In some patients relief was expressed in speech, and in others, in mental excitement, restlessness, and a tendency to be silly. Those who had suffered previous psychological conflicts which were poorly managed developed hypomania, depression, or phobias. In a few overly psychotic responses of brief duration were seen.

In a later communication these authors[144] divided the psychological responses into four grades, of which the first is a deviation of mood, usually elevation; the second, a quantitatively greater sense of euphoria. The third grade response subsumes typically psychoneurotic adaptations to stress; and the fourth grade, psychotic reactions, syndromes varying clinically in accordance with the organization of the patient's previous personality. Applying cybernetic patterns in the realm of neurological and psychological responses, they feel that the ability and the integrity of the organism is maintained by the harmonious integration of a series of interdependent buffer-like systems, each of which has its independent functions, but also is capable of provoking extensive changes in other systems—hence the error in limiting attention to one element of such a complex without regard for its influences and the consequences of such influences on all of the other components. There are certain features common to the reactions of all patients in whom these responses to ACTH occur. It is noted that the psychological reactions vary widely in degree, duration, and clinical form. The latter is chiefly determined by the previous organization of the patient's personality. The psychotic reactions tend to occur in patients who have made marginal psychological adjustments in the past. The more severe responses are associated with profound changes in the underlying physical disease. This may not necessarily be due directly to cause and effect. In some patients there is an intensification of the psychiatric symptoms which seems to coincide with marked shifts of the electrolyte balance. The authors note that the change from one dynamic level of adaptedness to another, even though in the direction of a statistically normal one, has not only physiological significance but considerable psychological meaning. The sudden cure of chronic illness is fraught with an equally significant loss of the secondary psychological gains of the illness. It is felt that this type of stress is as important, for example, as a decrease of 50 per cent in the concentration of the serum potassium in the

precipitation of the more severe psychotic changes noted. If it is true that psychological disorders affect approximately twenty out of 1000 individuals it would appear from the literature that the number of frank psychoses and psychoneuroses accounted for after hormone treatment, exceeds the expected frequency. There is, of course, a high incidence of marked psychological reactions, including psychoses in other glandular disturbances, and disorders such as hyperthyroidism and hypothyroidism, as well as in Addison's disease and in disturbances of the pituitary. It is not strange, therefore, that treatment with ACTH (when it induces a hypercorticalism) may also evoke psychological responses. A patient can only react within the framework of his own internal and external environments. It is especially necessary for the clinician to be thoroughly acquainted with all the component adaptative capacities of the patient to whom he is giving ACTH.

To return to the effects of ACTH on eosinophil cells, Rosenthal et al[145] show that although at the time of ACTH administration there is a marked diminution in the eosinophil cells seen in peripheral blood, those in the bone marrow are not decreased.

If in large doses ACTH prevents wound healing, in small doses its tendency in this regard may be used to prevent adhesions. Scheinberg and Saltzstein[146] use experimental animals, namely dogs and rats, and the known irritating effect of talcum powder. Doses of ACTH of 5 mg were sufficient to prevent the formation of adhesions without interfering with wound healing. It appears necessary, however, that the injections be continued for ten to fourteen days.

To show the effects of some of the buffer mechanisms involved, Schreier and Sattelberg[147] studied the influence of ACTH on amino acid metabolism. In their patient who suffered from nephrosis, there was (during an eight-day period of ACTH treatment) the usual marked increase in urinary excretion of 17-ketosteroids, nitrogen, and uric acid. Three hours after the injection of 20-30 mg of ACTH, the serum levels of isoleucine, leucine, lysine, methionine, threonine, tryptophan, and valine increased markedly, with the arginine level not changing. During the first twenty-four hours of treatment, the urinary excretion of ten amino acids was increased, with arginine and histidine excretion not being affected; but in the following days, despite continuous ACTH administration, the urinary amino acid excretion returned to normal.

Other metabolic changes confirmatory of some of those described above are reported by Segaloff and Many,[148] who demonstrated that in fasting phloridzinized rats adrenalectomy leads to a large decrease in the glucose and nitrogen excretion and complete suppression of ketone excretion. The excretion of glucose and nitrogen can be elevated by administration of 11-oxygenated steroids and desoxycorticosterone acetate. The levels are about half that seen in the intact controls. Such levels of ketone excretion can be raised to higher than those of intact controls with the administration of several other cortical compounds. ACTH leads to an increase in urinary glucose unaccompanied by an increase in nitrogen but accompanied by a substantial increase in ketones. These results are interpreted by the authors as indicating that the adrenal not only has an effect on gluconeogenesis from protein but also on fat breakdowns.

In order to study the metabolic effects of ACTH, preparations labelled with 131 I (100 microcuries) was injected intracardiacally into 250 male rats. Portions of various organs were examined for radioactivity of Bouin's solution in a Geiger tube. Within thirty seconds radioactivity

was discovered in the adrenals, blood, liver, spleen, and kidney and somewhat later on in the thyroid. There was little or no radioactivity after four hours, excepting in the thyroid in which the concentration steadily increased. Such concentrations were little affected by the amount of ACTH labelled with 131 I. When a similarily iodinated bovine serum-albumin preparation was given, the greatest degree of radioactivity was noted in the liver, spleen, blood, and kidney, with significantly less radioactivity in the adrenal. After four hours there was little fall in concentration of 131 I in most of the organs, and a much smaller increase in the thyroid. When the same amount of iodide (nonradioactive) was given, there was little concentration in any organ, excepting the thyroid. Radioautography was carried out on sections of the organs, in which case only the adrenal and thyroid gave positive pictures. In the adrenal there was more in the cortex, especially the inner layers. These experiments correlate the findings of other workers who discovered a proliferation of the two inner layers of the cortex after the administration of ACTH and the atrophy of such layers after hypophysectomy. The fact that a greater degree of localization did not occur in the adrenal may be due to the larger proportion of protein in the one preparation as compared to the other containing ACTH. The protein would be taken up by the reticuloendothelial system. The limited blood flow through the adrenal gland would also modify the results.

Further studies on the eosinophil response to ACTH in allergic states was done by Spellman [149] who studied a fifty-five-year-old patient suffering from contact dermatitis complicated by an exfoliative phase, the initial lesions becoming generalized after injections of poison oak extract. For the first treatment period ACTH was given intramuscularly every six hours for five days. During this time the eosinophil count fell from 162 to 131/cu mm. On the sixth day the drug was withdrawn for one week. There was a marked flare-up with an eosinophilia as high as 1,500/cu mm. Treatment was resumed with ACTH 10 mg q. 6. h. for three days and continued with 20 mg q. 6. h. for forty-seven days, during which time the dosage and interval were gradually tapered off. On the thirty-first day of this series of injections there was a fall of eosinophils from 1820 to 1270/cu mm four hours after the injection of ACTH/50 mg. The patient was kept on a low-salt diet and given potassium chloride, 3 Gm daily. The blood pressure, the acid-base balance, and the blood sugar remained within normal limits during the treatment period.

Probably the best paper on the physiological effects of cortisone and ACTH in man is by Sprague and his colleagues.[150] Of interest to us are the findings that ACTH increases urinary excretion of creatine and uric acid and, in some cases, gives rise to a negative potassium balance. The effects on sodium and chloride balances may vary, the usual pattern being retention of salt early in the period of administration followed by increased excretion when administration is prolonged. In some cases, there is a slight increase in urinary excretion of calcium and phosphorus. Studies of the urinary steroids reveal that the adrenal cortex when stimulated by ACTH secretes 17-hydroxy-corticosterone (compound F) rather than cortisone. A small percentage of administered cortisone is excreted in the urine as 17-ketosteroids and corticosteroids. The authors suggest that such terms as "side effects" or "toxic reactions" should not be applied to the physiological alterations induced by cortisone and ACTH, for they do not indicate the biological significance of these important substances. Every physician who administers either of these drugs should study this sixty-page paper in detail.

In another communication Sprague[151] discusses the clinical implications of the physiological effects of cortisone and ACTH administration. Although he stresses the fact that the urine of both diabetic and non-diabetic patients should be tested at intervals during the treatment period, he goes on to say that the fears that either may induce a permanent state of diabetes are apparently unfounded and that the presence of diabetes hardly constitutes a contraindication for the therapeutic use of ACTH in disorders in which it might be used with benefit. Sprague feels that as yet unknown physiological effects remain to be described and that those known to this date are not fully understood, little progress having been made toward correlating measurable physiological activity with therapeutic effects. The broadest understanding of the effects of ACTH and cortisone insofar as they have been described is necessary. He says, "There is no convincing evidence that the conditions which are thus favorably modified are actually associated with a deficiency of the adrenal hormones. Strong evidence indicates that this is not so."

In a later communication Sprague and his colleagues[152] again stress the necessity for a thorough understanding of the physiological potentialities of ACTH if they are to be used effectively in disorders requiring large doses or prolonged administration. Such effects are listed as those which occur in the metabolism of carbohydrate, protein and fat; of metabolism of water and electrolytes; of structure and function of the adrenal cortices; and as several miscellaneous hormonal effects. Awareness of the physiological potentialities is stressed as a prerequisite for the sage and effective use of the hormone.

Sprechler[153] makes some interesting observations as the result of the injection of ACTH into a series of patients of both sexes and all age groups suffering from a variety of acute and chronic disorders. The ACTH was from four different batches, and the dose varied from 30 to 100 mg q. 6. h. to q. 8. h., the treatment periods varying from four to 125 days. The urine was collected in twenty-four-hour lots and assayed for 17-ketosteroids, corticoids, and occasionally for glucocorticoids. In ten patients there was a normal response, the urinary excretions of steroids increasing on the first day of treatment and continuing to increase progressively to reach a maximum on the third to fifth day, remaining thereafter constantly elevated. Noteworthy is the fact that in four patients there was a poor response similar to that observed in Addison's disease, although none of the patients presented symptoms of this disorder.

One of the best reviews, although now two years old, is that by Thorn and his co-workers[154] whose complete paper on "The Clinical Usefulness of ACTH and Cortisone" deals with factual data on all aspects of the subject. It is generally available.

Venning and her group[155] show that the administration of ACTH in doses ranging from 60 to 210 mg to six normal individuals increases the total urinary excretion of neutral 17-ketosteroids from 44 to 105 per cent and the glucocorticoids from 72 to 565 per cent, the ketonic water-soluble reducing steroids being increased from 40 to 480 per cent. Studies on the various corticoid fractions, namely, the water-soluble ketonic, the water-soluble non-ketonic, and the benzene-soluble fractions, showed the greatest increase to occur in the water-soluble ketonic fraction. This was not, however, constant. Within six hours after the administration of ACTH, an effect on the steroid excretion could be observed; but in most cases the urinary steroids returned to normal levels within twenty-four hours following the last injection.

Wintrobe et al[156] reported on the effects of ACTH on forty patients with diseases affecting the hematopoietic system. Limiting this abstract to the tissue effects, none were seen other than manifestations of adrenal-cortical hyperfunction in one patient with portal cirrhosis, one with chronic idiopathic neutropenia, one with periarteritis nodosa, and one with anemia associated with chronic pyelonephritis. Striking clinical and hematological improvement occured in a number of patients, one of whom is listed as suffering from idiopathic thrombocytopenic purpura.

If any conclusions can be drawn from this summary on the effects of ACTH on the tissues they are that (1) all of the effects are not as yet known, (2) those studied indicate how widespread such effects may be, (3) the difference between "side effects" and physiological action depends on the point of view of the observer, and (4) all such effects depend to a greater degree than that seen in other methods of treatment on the physiological and psychological state of the patient.

ACTH AND IMMUNOLOGICAL MECHANISMS

Probably because clinical effects are quickly noticeable, while experimental work in the laboratory is time-consuming, the greatest number of references to the uses and results of ACTH deal with therapeutic phenomena, while the fewest are found in the field of immunology and those of its aspects of greatest interest to the allergist. This part of the field, therefore, will probably require future review.

In a careful study of the effects of ACTH and cortisone on certain immulogical mechanisms including reversed anaphylaxis, Arbesman, Neter, and Bertram[157] demonstrated that death from reversed Forssman anaphylaxis occurred in thirty-six of forty-eight control guinea pigs. Among those pretreated four to twenty-four hours before the shocking injection, it took place in eight of ten given 0.1 mg ACTH, eighteen of forty-nine given 0.5 mg ACTH, four of twelve given 2.0 mg ACTH, and in sixteen of eighteen given 6 to 20 mg ACTH. No such shock was noted in eight of the sixteen guinea pigs given 0.5 to 2 mg of a more potent ACTH preparation. Reversed anaphylaxis caused death in thirteen of twenty controls, in four of eight pretreated with ACTH 6 mg at one hour, and in two of twelve pretreated with ACTH/6-10 mg at four hours. There was little or no protection against direct active or passive anaphylaxis with either hormone. Both the antibody formation in rabbits and the development of active and passive sensitization were not altered by the administration of ACTH 12.5 mg four hours before, or 3 mg given four times daily after the sensitizing injection. It is noted that the reagin titer in the serum of man is unaltered by ACTH treatment.

Berthrong, Rich, and Griffith[158] sensitized forty rabbits with horse serum in a manner known to favor the development of periarteritis nodosa and cardiac inflammatory lesions. Half were given ACTH, the others serving as controls. In eighteen of the twenty untreated controls, there were well-marked vascular or cardiac changes, whereas such lesions were found in only five of the twenty animals treated with ACTH. The authors state that their results suggest that ACTH exerts an inhibitory effect upon the development of the cardiovascular lesions of hypersensitivity, but that further studies are required before any conclusion can be regarded as established.

Bjorneboe and his co-workers[159] studied the effects of ACTH and cortisone on the concentration of antipneumococcal antibody in rabbits. There was a reduction in such antibody formation. Both of the hormones

were administered in the beginning of immunization and after immunization was well advanced. Following ACTH administration they noted various types of mononuclear cells. Initially there appeared to be a phagocytosis of particulate or soluble antigen by cells of the reticuloendothelial system. Intense immunization is also known to be followed, at a later period, by enlargement of the spleen and lymph nodes. Antibody has been found in extracts of the lymph nodes draining the region injected with antigen prior to its appearance at other sites. The authors state, "At present it appears impossible to determine directly the cell type in lymphoid tissue which contains appreciable quantities of antibody. Discrepancies in the identification of various cells composing lymphoid tissue and the difficulty of comparing antibody concentrations in extracts of different tissues or fluids contribute to this problem. . . . Lymph nodes and spleen were found to contain measurable amounts of antibody and gamma globulins in contrast to the absence of these from thymus and tonsillar tissue." After discussing the changes known to occur following immunization, the authors show that their studies demonstrated a reduction in circulating antibody and in the lymphoid tissue following the administration of ACTH. It has been reported that the dissolution of lymphoid tissue by a single injection of ACTH results in a marked increase in serum antibody. This was thought to be an explanation of the anamnestic response. When quantitative immunochemical techniques are employed, however, no appreciable increase in serum antibody is found after a single injection of ACTH or cortisone despite a well-documented diminution in lymphoid tissues and lymphocytes. Indeed a decrease in the amount of circulating antibody has been reported. In addition, a normal anamnestic response was stimulated by homologous antigen in adrenalectomized animals. The authors state that the diminution in the antibody content of the serum observed in the ACTH and cortisone-treated animals may be the result of a negative nitrogen equilibrium. The changes they observed suggest an actual destruction of protein. An inhibition of synthesis of antibody would probably require more time to become as markedly manifest, since the half-life of antibody protein has been shown to be about two weeks. The reduction of circulating antibody apparently caused by ACTH and cortisone may have clinical significance in bacterial and allergic diseases. It is said, however, that it appears unlikely that the striking clinical effects noted with these hormones are ascribable to this action alone.

De Vries'[160] work showed that the administration of ACTH to previously immunized rabbits failed to produce a rise in circulating antibody levels despite a fall in the number of circulating lymphocytes.

Dews and Code,[161] whose work is familiar to all allergists, used two series of thirty-six and twenty-four guinea pigs, to one third of whom cortisone was given, and to one third ACTH, while the remainder served as controls. The hormones were used in moderate or large doses antecedent to sensitizing injections of egg white and given continuously while the sensitizing injections were administered and for some time afterwards. They reported that no treatment had any effect on the severity of the anaphylactic reactions induced by the subsequent intravenous injection of the antigen, although both hormones produced pronounced and sustained reductions in the number of circulating eosinophil cells in the blood of male and nonpregnant female guinea pigs. In another communication Dworetzky, Code and Higgins[162] had previously stated that neither cortisone or ACTH had any effect upon the degree of anaphylactic shock produced

in guinea pigs by the intravenous injection of the agent to which the animals had been sensitized.

Fischel[163] had previously shown that not only was there no alteration in the normal susceptibility of the guinea pig to anaphylactic shock when treated by ACTH but also that the hormone did not affect the Arthus reaction in rabbits sensitized with 0.02 to 0.22 mg of antibody nitrogen. Rabbits immunized to pneumococcus and given 0.5 to 1.0 mg ACTH presented about 50 per cent of the mean antibody level of the control group after fourteen and twenty-one days. The author concludes that at the present time, it appears that cortisone and ACTH do not alter the union of antigen with antibody as seen in a small number of rabbits immunized to pneumococci by a technique which usually results in the rapid production of large amounts of globulin, comparable in degree to that found in clinical hyperglobulinemia. It is the author's conclusion that whether the effect occurs at the level of antibody production, at the level of the union of antigen and antibody, or at any other point in the development of the immune response is not definitely established and should prove to be an interesting problem for further study.

According to Germuth and Ottinger,[164] the development of the Arthus reaction in rabbits given repeated intracutaneous injections of crystalline egg albumin is suppresed by the simultaneous injection of cortisone and to a lesser extent to ACTH. They state that there is a close correlation between the antibody nitrogen content of the serum and the severity of the skin reactions in both treated animals and controls, indicating that cortisone and ACTH diminish the production of antibody. Moreover, when antibody is injected intracutaneously, it was found that the Arthus reaction developed equally well in treated and untreated animals. They conclude that this demonstration that the hormones inhibit the development of the Arthus reaction by suppression of antibody formation is pertinent in view of the present emphasis on the general increased resistance to stress supposedly produced by treatment with these substances.

Studying humans, Long and Favour[165] found that in thirty-four patients given ACTH 40 to 200 mg daily for seven to ninety days, thirteen failed to develop a tuberculin reaction to intradermal tests with PPD after periods of treatment lasting seven to thirty days. Of these, seven developed local erythema when tuberculin tested prior to therapy while six had not been tested. Eleven showed positive and two showed negative reactions when tested after treatment was ceased. Five patients showed negative reactions before, during, and after treatment; while sixteen showed an alteration but not an obliteration of the positive reaction. In the same group, the reaction to an interdermal test with B-hemolytic streptococcus was abolished in nineteen. Nine had not been tested prior to ACTH therapy, but all had positive reactions after cessation of treatment. Patients who lost one type of skin reaction did not necessarily lose both, nor did the degrees of alteration under treatment uniformly parallel each other. Other inconstant results are reported. The size of the reactions varied from week to week, and the authors state that the significance of their observations is not as yet clear.

In her first communication of the effect of ACTH on the sensitizing and immunizing antibodies of inhalant allergy, Loveless[166] tested a patient suffering from atopic eczema, hay fever, and asthma observed during several months of ACTH treatment, the tissue susceptibility for three inhalant allergens being measured by controlled threshold tests of the conjunctiva, and the circulating antibodies being appraised in the skin

of a normal test subject. Although clinical improvement was marked within a few days and the conjunctival tolerance increased sixteen-fold for grass pollen, and four-fold for ragweed pollen and horse dander, no change took place in the reagin output for any of these allergens. All serological results seen on the fourteenth day after ACTH treatment were equal to the pre-ACTH end points. The patient was given a short, intensive series of booster stimuli in the form of 5,000 PNU units of grass pollen in divided doses during the third week of ACTH therapy. This raised the conjunctival resistance for this allergen eight-fold and produced a vigorous thermostable antibody response in almost the same amount as that noted in nine control similar patients receiving no ACTH. The point at which injections had to be terminated because of the development of mild systemic reactions was comparable to that of the control group. It is noted that the patient tolerated definitely more antigen in her immunization course than had three comparably allergic control patients who received no ACTH. Loveless concludes tentatively that ACTH inhibits the production of thermostable antibodies at four hours but fails to do so at ten hours, and that it raises the tolerance for injected antigen temporarily but not for ten hours. The clinical and conjunctival resistance seen as heightened by the hormone must occur beyond the antibody-forming or antibody-releasing tissue sites.

In a more detailed communication Loveless[167] discusses the influence of ACTH on the sensitizing and immunizing antibodies of inhalant allergy. It was first thought that ACTH effects a release of preformed antibodies from lymph cells within six to nine hours and that these immune bodies exerted a favorable influence on the host. A second hypothesis holds that the hormones alter the rate at which antibodies are formed following an antigenic stimulus. There is a third concept which holds that the union of antigen and antibody is in some way inhibited. It has also been considered that the site of action of ACTH takes place at some stage beyond the antigen-antibody combination, such as seen in the elaboration of inflammatory substances or the susceptibility of the effector cells to irritants. That the patient used for studies received enough ACTH was concluded from the fact that she showed not only clinical improvement but also a reduction in circulating eosinophils from 1023 to 391/cu mm and also developed such side effects as Cushing's facies, glycosuria, and a weight gain of twenty pounds. The injections of ACTH increased the tolerance of the conjunctiva sixteen times for timothy and four-fold for ragweed pollen. The circulating and sensitizing antibodies for timothy and ragweed pollen, however, remained unchanged in concentration as determined by serum dilution and antibody-exhaustion curves. Intracutaneous therapy for timothy pollen was then given, following which there was shown to be an eight-fold increase in tolerance by conjunctival tests with timothy pollen extract. The antibodies were not increased during immunization procedures with the two pollens, and the immunization with one pollen extract failed to alter the antibody output for the other. The patient presented the first instance in the author's experience where no thermostable antibodies could be provoked by a booster dose of 10,000 PNU given during a number of days or weeks. Loveless was unable to support the hypothesis that adrenal cortical activity leads to a release of preformed antibodies from lymphocytes through lysis. She observes that time may be a factor in that the ragweed pollen extract injections given this patient were administered four hours after ACTH injections while those of timothy pollen extract were given at about ten hours. She concludes from the

findings of previous workers that the antibody-antigen union as well as the subsequent elaboration of tissue-irritating substances like histamine and the susceptibility of nearby cells to these proteins all remain unaltered by cortical hormones, as seen in the guinea pig. It would appear from previous work that allergy in man is more closely analogous to anaphylaxis when it is seen in the dog and in the mouse than in the guinea pig. The conclusions to be drawn from this most important piece of work are that there is a definite increase in tolerance as judged by clinical improvement and lower conjunctival susceptibility following the use of ACTH, but no change in cutaneous susceptibility. There is no associated change in the concentration of sensitizing or thermostable antibodies after fourteen days of ACTH therapy as determined by passive transfer. The thermostable antibodies are produced with timothy pollen extract given about nine hours after ACTH 10 mg but not to ragweed pollen extract given about three hours after ACTH injection. The hormone may, therefore, have inhibited the immune response for a limited period of time. The amount of antigen tolerated in a "challenge" dose appears to be increased by the hormone at four but not at ten hours. The site of action of ACTH must, therefore, be at the level of union between antigen and antibody or at some point beyond this combination.

Mirick's work[168] concerned itself with pneumococcal polysaccharides in twelve patients with asthma and other disorders given 1 cc of the Squibb combination "A."

Antibodies as tested for by agglutination and mouse protection techniques were produced as promptly and in as high titer in patients receiving ACTH or cortisone as in controls. However, the degree of induced skin sensitivity to pneumococcus polysaccharide was depressed in some patients during hormone therapy. There was a consistent drop in the serum gamma globulin fraction of 1 to 60 Kunkel units in thirteen of fourteen patients whose values before ACTH treatment had been within normal limits. No consistent variation from the basal level of the gamma globulin fraction was noted in the serums of the control patients. Titers of anti-blood group substance, typhoid agglutinins, and C-reactive protein showed only slight or irregular fluctuations.

In a later communication, Mirick[169] reported on an additional thirty-seven patients in whom serum globulin was shown to have decreased in thirteen of seventeen taking ACTH injections. Agglutinins for typhoid bacilli were lowered four-fold to eight-fold in two of five patients, and isohemagglutinins were four-fold higher in four of eleven patients. The average dermal reactivity to pneumococcal polysaccharides was not depressed in eleven patients treated with ACTH or cortisone as compared with nine control patients. However, three patients treated with ACTH showed no dermal sensitivity despite the presence of abundant circulating antibodies. The results reported by other workers suggest that there is a species-specific difference in adrenal effects on plasma proteins and antibody formation, the rat more resembling man than does the rabbit.

Working with rabbits, Morrison, Ennor, and Thayer[170] injected ACTH 42 mg of two different preparations over a period of nine weeks. The animals showed no precipitable antibodies when titrated against the hormone or against crude hog pituitary extract. Serum from rabbits given Growth hormone 42 mg showed precipitable antibodies when titrated against Growth hormone as well as against a beef tissue extract prepared from skeletal muscle, adrenal and brain and a crude beef anterior pituitary

extract. The preliminary results indicate that Growth hormone is not species-specific.

To test the influence of the hormone on the mechanism of active infection, Orstov[171] injected mice with ACTH, following which they were given bread contaminated with twenty drops of a twenty-four-hour culture of paratyphoid B. Another group of mice infected with the same organism was treated with cortisone. Neither hormone showed any pronounced effect on the course of infections as compared with the control animals. Another experiment performed with mice each infected subcutaneously with *Staphylococcus aureus* organisms (50,000,000) and treated with ACTH or cortisone under identical conditions produced the same results.

In a discussion of the collagen diseases, Polley[172] notes that they have long been thought to be related to immune processes. There is an inverse relationship between the activity of the adrenal cortex and the amount of lymphoid tissue. It is readily recognized that the cortex is essential for proper maintenance of the organism in extremes of heat and cold, infection, and trauma. He stresses the fact that in any disease one must distinguish sharply between two distinct features: the tissue reactions (physiologic processes) which constitute the disease *per se*, and the residues of the disease (anatomic changes). ACTH and cortisone influence chiefly the inflammatory reactions of the active disease but not their residues. To use a figure of speech, they act as a fire shield but do not put out the fire; they do not act as carpenters to repair the damage. The results, therefore, will differ greatly depending on the stage of the disease present at the time each hormone is administered. He states that the hormones act at the tissue level—especially important and desirable to the ophthalmologist and the otolaryngologist—but do not kill bacteria. They do not "cure" the diseases, the symptoms of which they may suppress, but in some manner, perhaps simply by supplying extra adrenal hormone, they provide susceptible tissue with a shield against a wide variety of irritants.

Segal and Herschfus,[173] who reviewed the subject for this journal (December, 1950) analyzed the reports available at that time. In light of our present knowledge, their review is well worth rereading.

Confirmatory of some previous studies is the report by Sheldon and his associates,[174] who showed that ACTH modified but did not prevent the tuberculin skin reaction, although induration and inflammation were decreased. Guinea pigs with active tuberculosis were given ACTH for six days. Tuberculin tests on the fourth day elicited a definite reaction, but the effects in untreated guinea pigs were considered to be more pronounced.

Shwartzman, Schneierson, and Soffer[175] compared the effects of ACTH, cortisone, sodium salicylate, and calcium pantothenate upon the local tissue reactions produced in rabbits by injecting 0.25 ml of a meningococcus culture filtrate intradermally. The "provocative" dose was injected intravenously twenty-four hours later and caused a severe strongly positive local reaction in sixty-one of seventy-one control animals. Cortisone injected intramuscularly two hours before the "provocative" dose inhibited the reaction in four out of six rabbits, and ACTH similarly produced inhibition in fourteen of sixteen rabbits. Sodium salicylate was effective in seventeen of twenty-nine animals. Calcium pantothenate alone had no effect on the reaction but when combined with sodium salicylate it repressed the tissue reaction in all ten rabbits treated. Sodium salicylate augmented the action of suboptimal doses of cortisone. Their work suggests that sodium salicylate and calcium pantothenate may act indirectly

through the adrenal cortex, and that a clinical trial with these substances might also be undertaken in those diseases associated with alterations in vascular reactivity.

Sprague[176] whose review of the physiological effects of and clinical implications of ACTH has previously been mentioned, lists, with others, some of the papers abstracted in the present Progress Notes. He concurs with Rose and his associates, who suggest that although ACTH may alter the urinary secretion of histamine it is difficult to assess the importance of this effect in the allergic patient, since the relation of the excretion of histamine in the urine to the development and maintenance of the hypersensitive state is not known. He agrees that the point at which the site of blocking with ACTH occurs in the allergic process is not known, and that the experimental evidence suggests that the various components of the allergic mechanism which have been closely scrutinized are not influenced by these agents. It appears to him, therefore, that the site of action is at a tissue level, and that the influence of adrenocortical steroids on the permeability of membranes merits further consideration. He adds that there is some likelihood that the basic mechanism and action of the hormones in states of hypersensitivity may be closely related to their mechanism of action on inflammatory diseases of connective tissue such as rheumatoid arthritis.

White's[177] review of the role of adrenal cortex in immunity is undoubtedly available to all our readers. He questions whether the antibody-antigen reaction of tissues is limited to the very tissues in which the actual synthesis of antibody occurs. A general capacity of tissues for antibody uptake is confirmed experimentally by the simple procedure of incubating tissues from nonimmunized rats with antibody-containing serum from immunized rats. In all instances, the antibody content of the serum medium decreases and antibody is apparently taken up by all the tissues studied. The influence of the adrenal cortex on this process needs to be investigated and will be of interest in relation to a possible role of the adrenal in passive sensitivity and immunity. The adrenal cortex is listed as playing the following role in influencing immune mechanisms. First, the level of secretory activity of the adrenal cortex is influenced by the administration of an antigen, since antigens may augment, in a nonspecific manner, pituitary-adrenal cortical secretion. Secondly, an increased level of circulating adrenocortical steroids has a profound effect on cells of the reticuloendothelial system, namely, macrophages and lymphocytes, which are possibly concerned with the processes of antibody formation and release. Third, the rate of formation of antibodies by specific tissues is markedly influenced by the adrenocortical secretion itself. In addition, the adrenals may play a role in immune mechanisms by altering specific tissue permeability.

The paper by Zeller, Randolph, and Rollins[178] is familiar also to our readers. In their two patients with ragweed hay fever, the scratch tests with thirty-six common pollens and animal danders were not altered by ACTH therapy. Gross and histologic studies of passive transfer sites produced with serum before and after ACTH treatment presented the characteristic edema and eosinophilic infiltration. In the treated patients there was a decrease in eosinophil cells in ragweed wheals, which phenomenon paralleled the level seen in the blood of the same patients.

This discussion of ACTH and immune responses does no more than scratch the surface of a vast and unexplored field, one on which immunologists and allergists will be working for many years.

ACTH AND ITS SIDE REACTIONS

It is quite obvious from the literature that there is no strict line of demarcation between the physiologic, psychologic, and anatomic results of ACTH administration and its untoward actions. These, in any hormone possessed of such multitudinous immediate and long-range effects and in use for such a, comparatively speaking, short period of time, cannot by any means be fully known or measured. In the evaluation of no known drug is it so necessary to define the object of the observer or the state of the subject. Some of the so-called side effects because of the body's attempt to achieve homeostasis by "adrenal escape," may only be transient or unimportant. Those which are paradoxical, such as the repression of wound healing in a patient in whom a flattening of keloid scars may coincidentally occur, point up the complexity of the subject. For the moment (March, 1952), we can only say that as far as we know, based on the reports now available, the following phenomena, are, some of them, considered to be side reactions. The final definition must await the verdicts of further study, experience, and time. In this respect it might be well to ponder Whitehead's dictum that knowledge keeps no better than fish.

Some of the side reactions seen during ACTH administration have been listed in part in the papers reviewed above. The following references deal with what the authors themselves, in almost all cases, implied or referred to as side reactions.

Adlersberg et al[179] observed the development of hypercholesteremia during cortisone and ACTH therapy. Their patients demonstrated a consistent elevation of total serum cholesterol, esterified cholesterol, and phospholipids less uniformly than that observed following cortisone. All of the patients were kept on a regular hospital diet excepting for sodium restriction. In one patient with gout a low purine diet was used, and in one patient with amyloid nephrosis a Kempner rice diet had been prescribed. Eighteen patients received a total of twenty-one courses of ACTH, the duration of administration ranging from nine to 172 days, the total dose per course varying from 700 to 6,075 mg. The pretreatment total serum cholesterol varied from 132 to 289 mg/100 cc, with the esterified fraction constituting 68 per cent of the total serum cholesterol. The hypercholesteremia developed chiefly in those patients in whom there was an initial low serum cholesterol control value. The authors comment that the results of their study are consistent with the clinical experimental findings in the lipid metabolism of adrenal hypercorticalism. These observations may explain the premature atherosclerosis observed in Cushing's syndrome. Sustained hypercholesteremia in man has so far been produced only by suppression of normal thyroid function. A new hormonal mechanism is now seen as a second possible cause. It is interesting that in the members of the families of only two of the patients studied was hereditary hypercholesteremia demonstrated. It is suggested that the use of ACTH may convert a patient who has this familial predisposition from a latent to an overt case of hypercholesteremia. The fact that such changes occurred in 77 per cent of the courses of treatment makes this a most important consideration in the use of ACTH for prolonged periods of time in allergic subjects.

In his earlier communication Baker and his colleagues[180] demonstrated the induction of involution in the male reproductive system by treatment with ACTH. Rats were given 1 to 8 mg daily. There was a slight reduction in the weight of the testes, with atrophy of the Leydig cells in 80

per cent of the twenty-seven male animals studied. There was also reduction in the size of the seminal vesicles similar to that observed following castration. The changes seen included a loss of cytoplasmic basophilia and an increase in the concentration of glycogen.

In a later study concerned with wounds, Baker and Whitaker[181] showed that the direct application of adrenocortical steroids in a 25 per cent alcohol solution to cutaneous wounds delayed healing, although it did not completely counteract the stimulation to growth caused by cutting the skin. The effect was limited to the area of treatment. Whether these data are completely applicable to man remains to be determined.

The occurrence of peritinitis during ACTH administration is common knowledge, since Beck and his colleagues[182] first described it (1950). In disorders associated with fever, ACTH injections will often lower the temperature and pulse rate to normal levels within twelve to thirty-six hours. The omission of a single injection, a reduction of dosage, or the cessation of hormone treatment while the disease process is still active will result in an increase in the temperature and pulse rate. The use of ACTH changes the common hematological criteria used in diagnosis, since its injection causes both the sedimentation rate to return to normal and the total leukocyte count to decrease. Their patients, one suffering from Hodgkin's disease and the other periarteritis nodosa, both showed sufficient alteration of the presenting signs and symptoms to confuse the accurate diagnosis of an acute abdominal emergency. In the first patient there was no fever, a normal pulse rate, no leukocytosis and no rigidity. The only features of the underlying condition present were pain and an absence of peristaltic sounds. In the second patient the normal signs and symptoms were absent, except for a diminution in liver dullness and a rise in white cell count. In the first patient there developed a pneumococcal peritonitis and in the second the perforation of an acute ulcer. The pneumonia may have spread from a pulmonary lesion, and the ulcer may have been associated with a thrombosis. The absence of fibrin formation and adhesions (seen at laparotomy) may have been consequent upon the ACTH administration.

Mental disturbances, as occurring in patients given ACTH, have been reported upon by Clark and his co-workers.[183] Their paper reviews the previously reported side effects and, among others, status epilepticus, ulcerative colitis, and electroencephalographic and neuropsychiatric changes. Their ten case histories present four minor and six major mental disturbances. They omit the slight or moderate degree of euphoria, joviality, and optimism all seen following ACTH administration. In none of the ten patients had there been evidence of primary or secondary disease involving the central nervous system, nor were there metabolic changes intrinsic to the primary illness. In none was there a history of major mental illness. The psychological changes seen could not, therefore, have been anticipated or predicted. There was no correlation between the severity or duration of the psychoses and the average or total daily dose of ACTH. Among the changes seen were parasthesias, hazy and fuzzy sensations with transient muscle cramps and generalized weakness, marked anxiety and fear of death, marked depression, motor and intellectual retardation, impaired capacity for concentration and maintenance of sequential thought, an ill-defined feeling of detachment from reality, and psychic changes such as sarcasm and associability. Among the major changes were marked distractibility and emotional lability, with frivolity, weeping, and fragmentation of speech, hypomania, anorexia, insomnia, con-

vulsions, paranoia, marked hostility, depersonalization, incoherence and intellectual-affective disorganization. One patient became extremely overactive, hostile, assaultive, and destructive, with loss of self-identification and hallucinations paranoid in nature.

Cleroux[184] reviewed 225 patients treated by members of the Endocrine Department of the New England Center Hospital. One of the patients desribed his hunger reactions as "I have breakfast all morning, lunch all afternoon, and dinner all evening." In some patients the avidity for food was actually embarrassing. Mild euphoria was seen in 18 per cent of the patients and mental aberrations in a small number, with two patients developing depression and agitation, one patient becoming moody and distant. One complained of lightheadedness, and another, a widow, became obsessed with the conviction that she was pregnant. Approximately 30 per cent of the patients complained of insomnia, and a number of the patients, among whom were four with peptic ulcers, complained of epigastric discomfort. Urticaria was noted in those patients using Astwood's preparation "A." With the same preparation there were localized areas of redness and swelling at the site of the injections, with induration persisting for many days. There was mild pruritus, usually localized, occasionally present at the sites of previous injections. In a few cases there were increased sweating, mild headache, blurring of vision due to acute myopia, jitteriness, nervousness, palpitations, paresthesias, and numbness of the extremities. Four of the patients showed impaired wound healing. In one patient a chronic ulcer of the leg showed signs of regression. In some patients a leukocytosis up to 25,000/cu mm was observed. Convulsions occurred in four patients, and rounding of the face, acne, and hypertrichosis were seen in several with a cervicodorsal hump in two. Fourteen patients developed hypertension, and a few a transient slight glycosuria. In some patients there was pigmentation of the skin. Those who complained of muscular weakness were relieved by potassium chloride administration.

To stress the contradictory nature of the side reactions, Conn and his associates[185] observed a sharp fall in total serum cholesterol, with the rate of fall and the percentage of decrease greater in the esterified than in the free fraction. The free cholesterol levels returned to the base line values several days earlier than did the esterified fraction. They state that since adrenal cholesterol is rapidly depleted by stimulation, cortical activity during prolonged periods of stress may be severely limited by hepatic insufficiency and the related decrease in the capacity to esterify cholesterol.

Thromboembolic complications of ACTH treatment have been described by Cosgriff,[186] who observed twenty-eight such episodes in 700 patients, who, in all, had forty thromboembolic manifestations. Of these, nine were superficial and nine deep, fifteen were pulmonary, (fatal in two), and two were cardiac (fatal in one). Among the other thromboembolic phenomena noted were radial artery, mesenteric, and hepatic venous thromboses, each of which occurred once. Cerebral vascular accidents occurred twice. These episodes usually took place during the first three weeks of treatment but followed cessation of treatment in twenty-two, usually within the first fourteen days after the drug was withdrawn. Only four of the patients had previously experienced thrombotic episodes, two of them immediately before treatment was initiated. Three of the twenty-eight patients presenting such reactions subsequently received further courses of ACTH without ill effect. The average dose of ACTH was 40-80 mg. It is interesting to note that 75 per cent of the patients were between forty and seventy-

nine years of age, the group in which clinical thrombotic disease is usually seen. The author concludes that the vascular complications, together with the hypercoagulability of the blood, associated with the administration of cortisone and ACTH, indicate that thromboembolic side reactions should be considered as one of the serious complications of ACTH and cortisone therapy.

Further studies on the effect of ACTH on wound healing, this time in man, are reported by Creditor et al[187] who did elliptical skin biopsies on one patient with periarteritis nodosa and on another with rheumatoid arthritis, both of whom were treated with initial doses of 100 mg of ACTH and 40 mg daily thereafter. The areas were excised one week later and showed no microscopic evidence of healing in the mesenchymal tissues, with an absence of granulation tissue, leukocytes, fibroblasts, or proliferating blood vessels. One week after cessation of treatment normal healing was evident. In one patient irrigation of an experimental wound with hyaluronidase and penicillin produced gross healing in four days. A wound treated with penicillin alone did not heal.

For the side reactions listed up until June, 1951, the paper by Derbes and Weiss[188] should be consulted. Their communication discusses the physiologic relationships of cortisone and ACTH, as well as their effects upon electrolytes, the cardiovascular and the musculoskeletal systems, and neurological and gastrointestinal systems, as well as those observed in the skin, subcutaneous tissues, and mucous membranes, in sickness and in health. They conclude that to date none of the methods recommended to obviate side effects has been outstandingly successful.

Dorfman and his co-workers[189] describe status epilepticus as coincident with the use of ACTH in a thirteen-year-old boy suffering from an acute and progressive dermatomyositis. Epileptiform convulsions were seen in a six-year-old girl suffering from acute rheumatic fever and in a ten-year-old boy with periarteritis nodosa of two months' duration. Isolated convulsions also occurred in a ten-year-old girl suffering from disseminated lupus erythematosus. Since these patients were part of a group of forty children with connective tissue diseases treated with ACTH, the incidence is apparently 10 per cent.

In a paper discussing the effects of ACTH in a number of disorders, Elkinton et al[190] list the usual metabolic results as eosinopenia, low urinary sodium excretion, increased body potassium retention (with one patient showing a cellular deficiency of potassium resulting in hypokalemia), alkalosis, stupor, and areflexia (restored to normality by intravenous potassium infusion). In three of seven cases glycosuria, which was not severe, was seen. One patient showed a transient encephalopathy, manifested by coma, convulsions, and increased intracranial pressure. In one patient, the drug was discontinued because of the development of a Cushing's syndrome, and one patient developed a refractory state to ACTH and died. The authors state that there is much to learn concerning the therapeutic use of ACTH and cortisone. The series of complications encountered in their use makes this all too evident. Longer periods of observation will be required to assess the seriousness of such complications. Those encountered necessitate considerable caution in accepting the drugs for general therapeutic use, at least without careful clinical and laboratory supervision.

It was only a matter of time before allergy to ACTH would be described. Feinberg, Feinberg, and Bigg[191] present a case of generalized urticaria and angioneurotic edema, asthma and profound shock due to ACTH injection,

the patient being allergic to high dilutions. She was also sensitive to other pituitary preparations, the reactions being produced with dilutions as great as 1:10,000,000. The paradox that a substance which is presumed to improve allergic manifestations may be capable of causing them is resolved when we realize that the action of ACTH is delayed, and probably is never adequate to prevent severe allergic reactions. A twelve-day course of treatment with cortisone did not modify the allergic response to ACTH, indicating that it cannot be depended upon to provide protection against this type of allergy. In the patients previously described as ACTH-sensitive, the hormone derived from bovine origins did not produce skin reactions and was tolerated clinically, showing that this type of sensitivity is apparently species-specific. It is also interesting to note that the patient had an allergic reaction following the first injection of ACTH, with no history of having previously received pituitary substances. Skin testing showed her sensitive to Antuitrin, Pituitrin, Pitressin, and Pitocin. A positive passive transfer reaction was obtained to ACTH of porcine origin. No positive transfer reactions were demonstrable to the other pituitary substances.

The striking effect of ACTH in suppressing the manifestation of inflammation may, in some cases, actually increase the severity of, or enhance the susceptibility to, many infections. Finland, Kass and Ingbar[192] treated three patients with pneumococcal and two with viral pneumonia, with ACTH given along with and without antimicrobial agents. In all, clinical improvement, with defervescence and relief of symptoms as well as of the signs of acute toxemia, occurred promptly. In three cases there was no effect upon the organism. In one patient an extension of the pulmonary lesion and empyema occurred. The number of references to such side effects when ACTH is given during infectious conditions suggests that the utmost caution be used in observing the possibility of infections in patients taking these drugs, and that they never be used with antibiotics, since they may actually reduce the benefits derived from specific anti-infectious agents.

Methods of obviating the ill effects of ACTH have been considered. Because the ingestion of glucose enhances the response of hypophysectomized animals to ACTH, it has been suggested that the blood sugar level affects the action of ACTH on the adrenal cortex. Fortier, Skelton, and Constantinides[193] record the results of the study of adrenal cortical response to ACTH in hypophysectomized male rats under conditions of epinephrine-induced hyperglycemia and insulin-induced hypoglycemia. The ACTH was injected subcutaneously, followed by epinephrine and insulin at intervals of sixty and ninety minutes, respectively, so that the full action of ACTH coincided with the maximum hyperglycemic and hypoglycemic levels. Changes in blood sugar levels induced by insulin or epinephrine were not influenced by ACTH administration. Moreover, neither the epinephrine nor the insulin modified the effect of the ACTH on the liver glycogen and adrenal cortex, so that the alimentary hyperglycemia must be attributed either to an increase in the total store of carbohydrates or to an excessive production of intermediary metabolites.

For brief mention, since the subjects are considered in other papers, is Frank's[194] report on an acute psychosis developing during treatment with ACTH, and of the activation of tuberculosis as reported by Fred and his colleagues.[195]

Help in understanding the side reactions of ACTH can be obtained from the work of Hoagland et al[196] who present evidence that the adrenal

cortex is stimulated by ACTH released endogenously during electroshock therapy, and that the prognosis of improvement is correlated with the responsivity of the adrenal cortex to preshock test injections. In all, nine schizophrenic patients were studied. Four responded to a test dose of ACTH. Subconvulsive shocks of sufficient strength to produce a petit mal response clearly activated the adrenal cortex and did so more effectively than the injection of ACTH 25 mg. The authors feel that shock and insulin treatment both stimulate the pituitary-adrenal system and that the better both are, the more responsive the pituitary-adrenal system may be. They state that it is likely that in such patients ACTH will prove to have no therapeutic value and that the beneficial results of electroconvulsive therapy may be due entirely to other causes. Five schizophrenic patients treated for three weeks with daily doses of ACTH 100 to 200 mg showed no significant changes, except for transient improvement in one who later relapsed.

Hoeffer and Glaser[197] measured the electroencephalographic and neuropsychiatric changes in patients suffering from a diversity of disorders. These were subjected to most careful laboratory studies and showed the usual sodium and chloride retention, with associated water retention, potassium excretion, elevated serum carbon dioxide-combining capacity (with occasional hypochloremic alkalosis), decreased sodium and chloride in perspiration, increased gluconeogenesis with hyperglycemia, a diabetic type of dextrose tolerance curve, an increased deposition of liver glycogen, decreased serum inorganic phosphorus, falls in circulating eosinophils and lymphocytes (associated with leukocytosis), increased uric acid excretion, decreased serum cholesterol (free), increased calcium excretion, increased excretion of 11-oxysteroids, 17-ketosteroids and creatine, and a negative nitrogen balance. In some patients there developed acneform eruptions, hypertension, and hirsutism. In these patients there was no conclusive correlation between the electroencephalographic abnormalities and the changes in blood sugar or electrolytes. In six of the patients psychotic reactions occurred. Significant changes in the electroencephalograms took place in thirteen of the fifteen cases, and psychiatric changes (in two instances severe) occurred in ten of the fifteen patients. The powerful side effects which may accompany the therapeutic achievements of ACTH treatment are especially important in view of the necessity of planning long-range use of the hormone in chronic diseases.

Holley and McLester[198] noted manifestations of ascorbic acid deficiency shown as a hemorrhagic tendency in two patients. They state that although this syndrome is probably not of great frequency in the course of ACTH therapy, the possibility should always be considered when symptoms suggestive of scurvy appear during prolonged ACTH administration.

Jones and his colleagues[199] report the occurrence of acute nephritis following ACTH treatment of pemphigus.

The work by Finland (mentioned above) was continued by Kass and Finland,[200] who measured the effect of ACTH on induced fever. Patients were given varying numbers of killed typhoid bacilli intravenously before and after the administration of the hormone. Their temperatures were taken rectally every half hour until normal values were consistently obtained. It was discovered that the duration and intensity of the febrile response to the injection of typhoid bacilli in man was reduced by pretreatment with ACTH. That seen in rabbits given typhoid bacilli or influenza virus was similarly reduced. Although the mechanisms by which ACTH exerts its antipyretic effects is not clear, it is apparent from these

studies that this action of the hormone makes it possible that some patients will respond to its administration with defervescence, but with no alteration of the fundamental pathologic processes of the illness being treated.

The side effects so far described refer to intramuscularly injected ACTH. Following its *intravenous* use, in which smaller amounts are necessary, single doses are known to cause, at the most, mild chills and fever. In the studies by Mandel, Singer, and Gudmundson,[201] the patients were treated with intermittent intravenous injections and by continuous intramuscular drip. Eight of the twenty-five patients showed no untoward reactions. In the others eight presented a weight increase. Euphoria was present in five, hypertension in three, and a pyrogenic reaction in two, with restlessness in two, nausea and epigastric distress in one and gastrointestinal bleeding in another. Acne was present in three patients and mooning in four. Marked confusion and personality change occurred in two. The patients were treated for two to twenty-six days, with a daily dose of 1-20 mg, doses given over a period of eight to twenty hours. There were no patients refractory to subsequent treatment, and the total dosage necessary varied from one tenth to one twentieth of that previously injected intramuscularly. Eighty additional patients treated since the first report confirm the results here cited.

Merritt[202] has described his experiences with ACTH in diseases of the nervous system. Twenty-five patients with multiple sclerosis were given five days of pre-treatment with placebo medication and then two weeks of ACTH, followed by two weeks of placebos and then ACTH for an additional two weeks. There were no patients cured or significantly improved, excepting that a few showed improvement in strength and in an abatement of spasticity, with occasional improvement in bladder function and in eye movements. The sensory deficits were not affected. The author states that in view of the fact that the symptoms often disappear spontaneously in multiple sclerosis, occasionally dramatically so, it is necessary to conclude that ACTH does not significantly modify the lesions already present. No new symptoms occurred during treatment. He comments on the fact that various observers implicate an allergic factor in multiple sclerosis and that ACTH seems to prevent the development of allergic encephalomyelitis in monkeys, in whom the lesions resemble those seen in multiple sclerosis. He found ACTH ineffective in amyotropic lateral sclerosis and in progressive muscular dystrophy, in myotonia atrophica, in Wilson's disease, Parkinson's disease, epilepsy, and transverse myelitis. A patient with myasthenia gravis was made worse by ACTH administration. The variegated psychotic manifestations seen following treatment with ACTH do not correlate with the electroencephalographic abnormalities observed, the loss of the alpha rhythm, or the development of the slow, irregular wave activity, all of which are noted as transient phenomena.

Although the effect of ACTH on tuberculosis in man is known as a secondary side reaction, primary evidence is presented by Paraf and Desbordes,[203] who injected guinea pigs intradermally with the Koch bacillus and treated them fifty-eight days later with daily injections of ACTH 12 mg for two days. The animals were then reinjected with 5 mg (moist weight) of the bacillus. The control animals, similarly infected, developed typical Koch's phenomena, but those treated with ACTH generally presented rapid caseous and ulcerative degeneration, followed by caseous adenopathy. The aggravation of the tuberculous process usually observed in women during pregnancy, when the body is literally inundated with

steroids, including cortisone, is stressed. The authors conclude that ACTH, although it inhibits allergic reactions and may produce a modification of collagenous and reticuloendothelial tissues, may also permit rapid dissemination of pathogenic organisms.

How far-reaching the side effects of ACTH treatment may be is seen in the communication by Proctor and Rawson[204] who presented the first case report of irreversible damage to the fascicular zone of the adrenal cortex following ACTH injection. The patient, a negress of thirty-six, suffered from chronic cervicitis and lupus erythematosus. She improved for approximately seven days and then, with a second course, developed a pneumonitis and died. At necropsy the cells of the zona fasciculata showed nuclear pyknosis and absent cytoplasm. Because the lesions of the lupus erythematosus disseminata were relatively inconspicuous in comparison with the marked damage to the adrenal cortex, it was presumed that adrenal cortical failure was the cause of death.

Not all reports are so depressing. Renold, Forsham, Maisterrena, and Thorn[205] treated, in all, thirty patients with intravenous ACTH. An eight-hour intravenous infusion evidently stimulates the cortex for sixteen to twenty hours, so meeting the patient's daily requirements. By using a maximum of ACTH 20 mg daily, for eight hours in twenty-four, excessive stimulation of the adrenal cortex is apparently avoided. In all, one hundred patients and normal subjects were used. No anaphylactic reactions were noted, although the author states that patients should be watched for at least thirty minutes for evidence of allergic responses. Patients given an intravenous infusion thirty days after the end of a series of similar intravenous treatments showed a normal response without untoward reactions. The authors say, however, "it should be stressed that the period of observation in this series is, at present, too short to warrant a conclusive answer to the question as to whether or not drug resistance or unpleasant allergic phenomena might occasionally develop after long intervals have elapsed." It is stated that the side effects are analogous to those observed with intramuscular ACTH, but these are not listed. It is suggested that, providing the patient is kept under observation during the early part of the infusion, the method may be considered safe.

Rome and Braceland[206] describe the range of psychological responses to ACTH as falling into four clinical grades: (1) deviations in mood, usually elevation, (2) intensification of the first grade to euphoria, (3) psychoneurotic reactions, (4) psychotic reaction types. If one accepts as valid as the hypothesis that some psychiatric disorders are related to altered function or effects of anterior pituitary-adrenal cortical activity, the nature of events in a psychotic reaction following administration of these hormones is significant. Under certain circumstances each is capable of provoking profound changes in the other. Each physiological and psychological factor acts as a vector, having dimensions of magnitude and direction unique for the individual, although certain common features of psychological responses have been observed. These include (1) wide variation in response, the clinical form being largely determined by personality organization; (2) a tendency for psychotic reactions to occur in patients with previous marginal psychology; (3) the usual association of grades 3 and 4 responses with profound change in underlying disease; (4) lack of consistent correlation between metabolic changes and psychiatric syndromes; (5) sudden or great change implying a different level of adaptiveness, rather than kind of change; (6) a psychological as well

as physical impact of change of dynamic level of adaptiveness. Their evidence points to a higher incidence of psychiatric disturbances after steroid treatment than that which occurs in the general population. Because the capacity to adjust is a function of multiple factors in the present and past life of the patient and in the internal and external environment in which he lives, his reactions may cover a wide range. In view of these potential complications of ACTH therapy, it is necessary to be cognizant of all the adaptive capacities of any one patient.

Rule[207] (in a letter) underlines some of the dangers of ACTH treatment. A patient in whom signs of pituitary insufficiency had developed after the birth of twins, was admitted to the hospital with high fever, sore throat, nausea, and vomiting which improved with penicillin and supportive therapy. On the third hospital day she was given ACTH 25 mg, and the following morning she was found dead. Autopsy revealed marked atrophy of the adrenals, thyroid, ovaries, and uterus, the pituitary revealing a large mount of fibrous tissue replacement. The clinical pathological findings indicated the presence of long-standing anterior pituitary and secondary adrenal hypofunction, the septic sore throat probably causing further adrenal exhaustion. One of the criteria of ACTH treatment should certainly, therefore, be proof of normal adrenal function.

The complexities of the physiology of the pituitary-adrenal system are pointed out by Russell,[208] who mentions, among other things, the effect of ACTH as causing an increase in the excretion of uric acid, for which the reason is not known. A purely renal action on uric acid excretion has been suggested. Although many workers confine their studies to the effect of ACTH on lymphoid tissues and eosinophil cells, it is probably that the effects are widespread in all tissues of mesenchymal origin. Russell does not like the terms "resistance" and "adaptation," which she feels are words mainly used to cover ignorance. What is known is that in adrenal insufficiency the subject is sensitive to all untoward influences: namely, cold, heat, trauma, infections, toxins, drugs, hemorrhage, and hypersensitivity reactions, from which he can be protected by active adrenal steroids. In cases of trauma and anoxia, although these are stress factors, the hormone is of little help. After critically examining the evidence given by the variety of methods used to obtain some idea of the relative rate of adrenal hormone secretion, Russell states that the rate of secretion of ACTH, and hence of the adrenal hormones, is not at all constant, but is much increased by almost any stimulus or change in internal or external environment. Mild degrees of stress may suffice to stimulate the pituitary. In some animals, quiet handling alone will have the same effect, as judged by lymphocyte and 17-ketosteroid responses. Among other common types of initiating stimuli are exercise, pain, and emotional upsets, as well as allergic responses, infection, and the like. Adrenal hormone secretion is not an all-or-nothing process, simply necessary for the well being of the body, but the pituitary-adrenal relationship constitutes a most reactive system. Experiments have shown that the amount of hormone put on in adrenal vein plasma as assayed biologically as *per hour* several times the amount which can be extracted from the gland after its extirpation. Russell states, "We do not know the degree of increase in the rate of secretion after any unusual provocation, but it must be very large. There is then, here, a considerable margin for error, so to speak, in our estimation of what is normal adrenal function. Future work should tell us whether, in treating disease states with adrenal hormones, we are employing a pharmacological action of these substances or, in fact, are eliciting a true physiological response."

Selye[209] has studied the effects of ACTH and cortisone on resistance to infection. His animal experiments show that death usually occurs as a result of unbridled bacterial proliferation, usually beginning in the lungs and leading to pulmonary abscess formation with general septicemia and abscesses of the liver, spleen, kidneys, and sometimes other organs. Of interest in this paper is the report that fatal systemic infections can occur with presumably otherwise nonpathogenic micro-organisms, such as are normally present in the body, and that these effects of ACTH can be completely prevented by suitable doses of purified somatotrophic hormone.

The effect of ACTH on urinary gonadotropin excretion has been studied by Sohval and Soffer.[210] The usual daily dose was ACTH 100 mg. The total treatment period varied from two weeks to many months and was continuous on a maintenance basis, especially in the patients with disseminated lupus erythematosus. In nine patients there was an excessive quantity of urinary gonadotropin. In six patients in whom pretreatment levels had been determined, the increase was 60 to 240 mouse uterine units per twenty-four hours. The increase could not be correlated with race, age or sex, the nature, duration or acuteness of the disease, type or duration of therapy, clinical response, or the data derived from laboratory studies of the patient's electrolytes and protein and carbohydrate levels.

Of a group of seventy-nine patients treated with ACTH by Smythe,[211] three presented an activation of peptic ulcer. Previous reports concerned a patient with periarteritis nodosa, on whom an exploratory laparotomy was done because of the clinical evidence of peritonitis. The second patient previously reported had severe abdominal pain nine hours after cessation of ACTH therapy. X-ray demonstrated a deformed duodenal bulb with deep ulcer crater. Smythe's own report is concerned with a male patient who was known to have a quiescent ulcer and was given ACTH for lupus. No ulcer symptoms had been present since 1941. On the twelfth hospital day the patient complained of sharp, stabbing pain in the right upper quadrant. He died on the fifteenth hospital day, the peritonitis present being resistant to all forms of treatment. The second patient free of ulcer pain since 1948, was given ACTH for psoriasis of both the skin and the joints. Following this treatment one ulcer was reactivated. The third patient suffered from mycosis fungoides and psoriasis. There was a suggestive history of peptic ulcer. He also after two days of treatment, was stricken with a sharp, excruciating pain in the epigastrium, with reactivation of the ulcer, proved by x-ray. The author comments that "the effect of ACTH may be due, not only to its depression of wound healing, but also because it may increase uropepsin excretion, usually high in peptic ulcer patients, although not related to gastric juice pepsin." The author believes that there is enough evidence at the present time to warrant caution in the use of ACTH in patients with a history of peptic ulcer.

Two patients studied by Stafanini and Rosenthal[212] developed, while taking ACTH hemorrhagic manifestations, presumably due to an ascorbic acid deficiency. The diagnosis was based on hemorrhagic manifestations following minimal epidermal trauma, a low plasma ascorbic acid level, and a low urinary excretion of ascorbic acid, as well as a low plasma ascorbic acid tolerance curve. They point out that although such ascorbic acid deficiency is probably not common during the course of ACTH therapy, it should be considered if hemorrhagic signs appear during its prolonged administration.

In a series of 128 patients studied by Steinbrocker[213] et al, 40 per cent

displayed side reactions. Glycosuria, with or without hyperglycemia, occurred in eighteen and persisted in two (due to latent diabetes); edema occurred in sixteen, imposing a discontinuance of treatment in two; mooning was seen in twelve, and skin reactions in thirty; menstrual disturbances occurred in four; constipation and abdominal cramps were present in six; one patient had a perforation of a duodenal ulcer. Vascular disorders occurred in fifteen, all but one of whom were in the fifty-to-eighty-year-old group. Psychic changes, shown as euphoria, occurred in fourteen; insomnia in four, and psychotic symptoms in seven. Transient hypertension was present in five, congestive failure in one, and coronary insufficiency in another. Seven patients presented evidence of thrombophlebitis, with peripheral arterial occlusions in one; transient hemiplegia in one; paresis in two; and paresthesias in two others. Three patients were asthenic. Osteoporosis with vertebral compression was seen in one, and fracture in another, both considered as due to ACTH treatment. The authors list the contraindications to ACTH as tuberculosis, cardiac failure, severe diabetes, psychotic episodes, severe psychoneurosis, severe hypertension, infectious diseases, malaria, severe osteoporosis; and they consider ACTH relatively contraindicated in diabetes, hypertension, compensated cardiovascular disease, severe varicosities, phlebothrombosis, obliterative arterial disease, osteoporosis, and neurosis. They feel that in elderly patients hospitalization is imperative.

Sulzberger et al,[214] as a result of studying forty-four patients given ACTH treatment, list the side reactions as follows: increased localized or generalized pigmentation in twelve, mooning in nine, hyperglycemia in two, furunculosis in one, ankle edema in four, transitory toxic psychoses in two, and a multiform erythematous eruption, with fever and malaise, in one.

In summary, we can evidently say that side reactions due to ACTH treatment will affect carbohydrates, protein, and fat metabolism, and will have androgenic and anabolic effects, as well as endocrine depressive results on the thyroid gland and the gonads. In the tissues ACTH will affect the mesenchyme, the lymphoid tissues, the lymphocytes, the eosinophils, and the erythrocytes. In hypersensitivity states it may inhibit the development of arteritis and cardiac lesions which might otherwise follow the injection of antigens into sensitized animals. It may cause a remission of clinical symptoms of various bacterial infections, although it does not destroy the active foci of infection, which may become active following cessation of therapy. It inhibites the reactivity of tissues, it stimulates the central nervous system in the direction of an exaggeration of the patient's basic personality structure, by acting directly on the pituitary-adrenal axis or indirectly by electrolyte or metabolic imbalance.

It is contraindicated in congestive heart failure (excepting in some patients with rheumatic heart disease), chronic nephritis, hypertension, diabetes mellitus, peptic ulcer, psychoses and psychopathic personality states, tuberculosis, and endocrine disturbances such as Cushing's syndrome, acne, and hirsutism. It is useless in Addison's disease.

It may be useful, especially while studies are being conducted, in bronchial asthma, severe nasal allergy, contact dermatitis, atopic eczema, and drug sensitivities, especially when the causative allergens have been removed. It may help some patients with urticaria and angioneurotic edema.

ACTH has not, in any sense of the word, helped us discover the cause of allergic disease. As a matter of fact, did anybody, anywhere, ever think it would?

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75 Bay State Road

News Items

INTERNATIONAL ASSOCIATION OF ALLERGOLOGY

On the morning of May 11 a meeting was held at the Pont-Royal Hotel, Paris, by the members of the committee of the IAA who were attending the Paris celebration of the fiftieth anniversary of the discovery of anaphylaxis. Those present were Fred W. Wittich, U.S.A., President; Bernard Halpern, France, Secretary-General; Arthur S. Grumbach, Switzerland, Treasurer; D. A. Williams, England, Third Vice President; and Egon Bruun, Denmark, Member-at-large. Many unofficial recommendations were made for implementing the Second Congress on Allergy to be held at Rio de Janeiro, Brazil, during the summer of 1955.

SECOND EUROPEAN CONGRESS ON ALLERGY

The Danish Society for Allergological Research announces that the Second European Congress on Allergy, according to the proposal given to the Northern countries in Paris in 1950, will be held in Copenhagen from May 21 to May 23, 1953, under the presidency of Dr. Ernst B. Salén, Stockholm, Sweden.

The subjects proposed for discussion are (1) Allergy and Adrenal Hormones, and (2) Allergy and Infection. A detailed program with the names of the speakers will be published in due time.

Pan-American physicians are cordially invited to attend and participate in the discussions. For further information, write to the secretary-general, Dr. Egon Bruun, Østergade 18, Copenhagen, Denmark.

AMERICAN ACADEMY OF ALLERGY

The 1953 annual meeting of The American Academy of Allergy will be held in Boston at the Hotel Statler on February 26, 27, and 28. Titles and abstracts not exceeding 200 words should be sent in quadruplicate to Walter S. Burrage, M.D., 208 East Wisconsin Avenue, Milwaukee 2, Wisconsin, before October 15. Completed papers may be submitted to the Editor of the *Journal of Allergy* prior to the meeting, and all papers read at the meeting must be submitted for publication.

AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

The annual meeting of the American Society of Ophthalmologic and Otolaryngologic Allergy will be held at the Palmer House, Chicago, on October 17, 1952. Officers of the society are Hugh A. Kuhn, M.D., F.A.C.A., Hammond, Indiana, President; Kenneth L. Craft, M.D., F.A.C.A., Indianapolis, President-elect; Russell I. Williams, M.D., Associate, ACA, Cheyenne, Wyoming, Vice President; and Joseph W. Hampsey, M.D., F.A.C.A., Pittsburgh, Secretary-Treasurer.

The Instructional Course in Otolaryngologic Allergy given by the Hansel Foundation is tentatively scheduled for the week of May 31, 1953.

POSTGRADUATE COURSE IN PEDIATRIC ALLERGY

Under the direction of Bret Ratner, M.D., F.A.C.A., Professor of Clinical Pediatrics and Associate Professor of Immunology, and members of those departments, at New York Medical College, Flower and Fifth Avenue Hospitals, a postgraduate course in pediatric allergy will be offered November 5, 1952, through May 31, 1953. There will be thirty sessions, Wednesdays 9:00 a.m. to 4:00 p.m. The fee is $300.

This course consists of lecture-seminars, laboratory and clinical procedures, clinic

work, ward rounds, and animal experimentations. Lecture-seminars cover the basic principles, diagnosis, and treatment of allergy in children, as well as applied immunology. Applicants must be certified in pediatrics or have the requirements for certification. The group will be limited. Application should be made to the Dean, New York Medical College, 106th Street and Fifth Avenue, New York 29, New York.

Fellowship Available.—A one-year Research Fellowship in Pediatric Allergy is also available starting January, 1954. Application should be made now.

COURSES IN ALLERGY, COOK COUNTY GRADUATE SCHOOL OF MEDICINE

Readers of the ANNALS are reminded of courses in allergy given continuously at the Cook County Graduate School of Medicine, 707 South Wood Street, Chicago 12, Illinois. Three courses are presented by Leon Unger, M.D., F.A.C.A.: (1) a one-month course, full time, in which the student works in Doctor Unger's office, takes didactic instruction, and goes to Wesley and Cook County Hospitals; fee $200; (2) the same course as (1) but extended over a period of six months; fee $500; (3) a ten-week instructional course which begins every April and October, meeting every Wednesday from 10:00 a.m. to 4:00 p.m., in Doctor Unger's office; the course is open to any practitioner; fee $125.

CALIFORNIA SOCIETY OF ALLERGY

At the 81st Annual Session of the California Medical Association, Los Angeles, the following officers of the California Society of Allergy were elected for the year 1952-53:

President—M. Coleman Harris, M.D., F.A.C.A., Vallejo
President-elect—Grace M. Talbott, M.D., F.A.C.A., San Francisco
Secretary-Treasurer—Norman Shure, M.D., F.A.C.A., Los Angeles

NEWS ABOUT ACA MEMBERS

Frederic Speer, M.D., F.A.C.A., of Kansas City, Kansas, has been appointed Instructor in Pediatrics at the Medical School of the University of Kansas.

* * *

M. Coleman Harris, M.D., F.A.C.A., Los Angeles, Director of the Allergy Clinic at Permanente Hospital, has been named Chairman of the Allergy Section, California Medical Association, as well as being elected President of the California Society of Allergy.

* * *

With regret we announce the death on July 8, 1952, of Elisabeth M. Weil, M.D., wife of A. J. Weil, M.D., F.A.C.A., Pearl River, New York. Dr. Elisabeth Weil, besides practicing dermatology in Pearl River, was a staff member of the Department of Dermatology, Vanderbilt Clinic, Columbia-Presbyterian Medical Center, New York City. The College sends sincere sympathy to Doctor Weil in this time of loss.

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ACA members are urged to send in news items to the Managing Editor, ANNALS OF ALLERGY, 401 LaSalle Medical Building, Minneapolis 2, Minnesota.

* * *

Paul Kallós, M.D., F.A.C.A. (Hon.) of Helsingborg, Sweden, has received a research grant from the Swedish Royal Medical Board which will allow him to continue his serological and clinical investigations of baker's asthma and the chemistry of flour-allergens.

BOOK REVIEWS

ANTIBIOTICS. By Sir Howard Florey, Ph.D., Sir William Dunn School of Pathology, Oxford. 35 pages, 22 figures. Price $1.50. Springfield: Charles C Thomas, 1952.

This monograph represents the fifty-second Robert Boyle lecture delivered before the Oxford University Scientific Club. This booklet is replete with excellent photomicrographs illustrating culture methods and procedures. The lecturer demonstrates his acquaintance with chemistry and the different aspects of biology necessary to understand the nature of the antibiotics and condenses the information in a remarkable manner. Most physicians using the antibiotics will be interested in reading this fascinating story of their development.

A HISTORY OF THE AMERICAN ACADEMY OF PEDIATRICS. By Marshall Carleton Pease, M.D. 302 pages. Sponsored by the Borden Company, New York.

Not only pediatricians but all physicians should be interested in this comprehensive history of the American Academy of Pediatrics. It represents a vast amount of research of the literature covering the whole subject of pediatrics and everything pertaining to the growth and development of the Academy since its formal organization in 1930. During these twenty-two years there has been rapid progress in the specialty, and this history brings forth the accomplishments of certain pediatricians greatly responsible for shaping the policies and destiny of the Academy. The project was financed by a grant from the Borden Company, and copies of the book were distributed to all members of the Academy.

Dr. Pease deserves great credit for this comprehensive collection of data and the way he has presented the material in such an interesting manner, including descriptions and photographs of outstanding personalities who aided in the development of the Academy. As is often the case, the many men who belong to an association have little knowledge of the real achievements of that association until brought to their attention in a forcible manner.

Part 1 of the volume deals with the constitution and by laws, the central office, and the financing of the Academy. It lists all the officers, committees, various state chairmen, the membership roster, and the meetings. Part 2 presents the function of the various committees organized to develop pediatric medical education, as well as a full description of the history and publications. Part 3 deals with the development of the children's bureau, the expanding program, the relation of the A.M.A. to the Academy, the background of child health study, and the author's predictions for the future.

TOBACCO AND THE CARDIOVASCULAR SYSTEM. *The Effects of Smoking and of Nicotine on Normal Persons.* By Grace M. Roth, Ph.D., Associate Professor of Experimental Medicine, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota; Consultant in Section on Physiology, Mayo Clinic, Rochester, Minnesota. 66 pages, 9 figures. Price $2.25. Springfield: Charles C Thomas, 1951.

Those who are personally familiar with the many years of devotion by the author to observing the effects of drugs or toxins or physical agents on the cardiovascular system will particularly enjoy this little monograph. With the rapid increase in the use of tobacco, it is timely that an authority such as the author publish her observations. The volume contains nine chapters, covering aspects of the smoking problem, factors which influence the measurement of peripheral blood flow in the extremities, a

standard smoking test, consistency of results, importance of habituation and of nicotine, and effect of smoking on induced dilatation of the peripheral blood vessels. Her conclusions may cause one to hesitate to continue the habit of smoking: "In normal individuals the usual vascular effects produced by the smoking of tobacco are a rise in the blood pressure and pulse rate with simultaneous constriction of the peripheral blood vessels of the extremities as measured by a decrease of skin temperature. Habitual smokers do not develop such tolerance to tobacco as to avoid the vascular effects produced by smoking. . . . The vascular effects are produced by the nicotine in the smoke. More pronounced effects are present when the smoke is inhaled and the tobacco is moist. Analogous effects on the heart and blood vessels of the extremities can be produced both by smoking tobacco and by the intravenous injection of nicotine. By decreasing the amount of nicotine in cigarettes the vascular effects can be reduced, but the amount of nicotine in the available denicotinized cigarettes is not sufficiently decreased to protect against the effect of smoking them. Acceptable evidence is available that drinking a cocktail will not necessarily nullify the effect of smoking."

The binding of both these monographs is attractive and durable, and the format is of the usual high quality of the publisher.

THE PATHOGENESIS OF TUBERCULOSIS, Second Edition. By Arnold R. Rich, Johns Hopkins University School of Medicine, Baltimore. 1028 pages, 105 illustrations. Price $15. Springfield: Charles C Thomas, 1952.

In its first edition, Rich's *Pathogenesis of Tuberculosis* acquired a high reputation both as a systematic and painstakingly documented presentation of the enormous wealth of data on tuberculosis infection and as an analysis of this evidence. The book has been out of print for some years, and the present publication of a second and revised edition fills a real need. New information accumulated since the first edition in 1944 has been incorporated into the body of the text. References now number 1,500. Thus as a guide to the original sources of evidence and to the history of viewpoints, this presentation is without rival. The argumentation is tempered throughout by the author's extraordinary first-hand experience in almost all the phases of the complex problem. For the allergist, the sections on tuberculin sensitivity in all its ramifications offer particularly rewarding reading.

PENICILLIN DECADE, 1941-1951. Sensitizations and Toxicities. By Lawrence Weld Smith, M.D., Medical Director, Commercial Solvents Corporation, and Ann D. Walker, R.N. 122 pages. Price $2.50. Washington, D. C.: Arundel Press, 1951.

This is a timely monograph on the sensitization and toxicities reported in the literature following ten years of clinical use of penicillin. The discussion ranges from the vegetable mold *(P. notatum)* cultivated by Fleming in his original crude broth filtrate to the highly purified crystalline penicillin of today.

The first chapter reports sensitizations and toxicities throughout the development of penicillin. Many of these reactions are on the basis of an allergy, such as urticaria, contact dermatitis, serum sickness, anaphylaxis, exfoliative dermatitis, and ophthalmic and oral reactions. The toxicity of various preparations such as beeswax-oil preparations is discussed. The remainder of the book covers obstetrical reactions, pediatric problems, renal irritation, central nervous system changes, spinal cord involvement, the Jarish-Herxheimer reaction, miscellaneous reactions, antibodies, blood culture, bacterial resistance, and—of most importance to the allergist—penicillin as an allergic hazard.

Many writers have pointed out the increased reactions to penicillin, not only in number but in gravity. The familiar urticaria is being replaced by reactions that resemble serum sickness, suggesting that an anaphylactic phenomenon, which is

always dangerous, has now resulted. Reactions that appear after a definite presensitization and that follow after a longer refractory period are characterized by chills, fever, prostration, arthritic symptoms, and shock. "It can readily be postulated that serious allergic manifestations are significantly present while morbid and irreversible changes in the collagen reticuloendothelial structure can follow."

In view of the increasing indiscriminate use of penicillin, a warning is issued against considering this antibiotic as a cure-all or using it to prevent infection, such as routinely before all operations, dental and surgical. It should always be kept in mind that antibiotics are of value only for the treatment of infections due to organisms sensitive to the specific antibiotics being employed.

The monograph is an objecive report of data relating to side effects following penicillin during the past decade of clinical use. The search for improved preparations continues.

THE 1951 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY. Edited by Marion B. Sulzberger, M.D., Professor and Chairman, Department of Dermatology and Syphilology, New York University Post-Graduate Medical School; and Rudolf L. Baer, M.D., F.A.C.A., Associate Professor of Clinical Dermatology and Syphilology, New York University Post-Graduate Medical School. 465 pages, 61 illustrations. Price $5.50. Chicago: Year Book Publishers, 1952.

This popular year book continues to abstract and review new diagnostic and therapeutic procedures pertinent to the type of cases seen most frequently in this field of practice. During the past few years there has been steady progress in our knowledge of ACTH and cortisone and related steroids. Based upon three years' experience in dermatology with these hormones, there is a better understanding of the dosage to be used in each type of dermatosis and the contraindications. Experience with the oral administration of cortisone, with the intravenous slow drip method of administering ACTH, and with the depot therapy with ACTH in slow-absorbing gels is increasing, and the advantages of these newer modes are pointed out. It is concluded that the topical application of these hormones is disappointing. The present year book deals with many other items reporting substantial scientific progress, including the use of radioactive isotopes, newer and older antibiotics and vitamins, fundamental newer studies differentiating between melanogenesis in benign and in malignant pigmented growths, studies on basic phenomena influencing the loss and the regrowth of hair, and studies on the control of tropical skin diseases and venereal diseases.

There is a timely article on some common errors in the diagnosis of skin diseases which is a guide to the general practitioner.

The book is divided into twelve topics covering treatment and prevention of skin diseases, x-ray and other physical therapy, eczematous dermatitis and urticaria, allergy, drug eruptions, hematogenous dermatoses, cancers and tumors, and venereal diseases. There is a complete index, and the figures are clear and informative.

CORRECTION

We wish to correct a news item which appeared in the May-June issue of the ANNALS. Owing to an unintentional oversight, in the list of the American allergists attending the IAA meeting who were honored in Zurich September 28, 1951, by Mr. and Mrs. Porter Kuykendall, the American Consul General, by a reception and cocktail party at their chalet, the names of several of those present were omitted: Drs. William Kaufman, Arnold A. Rich, Louis Schwartz, James J. Smith, and Lt. Col. Arthur J. Berger.